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## THE INTRARENAL ARTERIAL PATTERN IN THE NORMAL AND DISEASED HUMAN KIDNEY

*A Micro-angiographic and Histologic Study*

By

ARNE LJUNGQVIST

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# Introduction

For an accurate interpretation of the functional characteristics of the normal and diseased kidney a knowledge of the normal intrarenal arterial pattern and of the changes that this displays in renal disease is essential. Such a basis has not been provided by earlier studies as they have not included a comparative examination of the angioarchitecture and the histologic picture of the same specimen. As a consequence no reliable study of the intrarenal arterial pattern in the pathologic kidney has been performed and little light has been thrown on the course of the intrarenal arteries through the renal tissue and on their relation to the other structures, even of the normal kidney.

To explore the intrarenal arterial anatomy in the normal and diseased human kidney an investigation has therefore been carried out in which specimens were examined by both stereo-micro-angiographic and histologic techniques. In the normal kidney a progressive change in the intrarenal arterial pattern of the adult with age was found. To obtain a more comprehensive picture of the normal pattern at different ages the development of the intrarenal arterial tree from the fetal stage to adulthood was followed. On the basis of the findings relating to the normal kidneys a study was made of kidneys from cases of essential hypertension and of chronic pyelonephritis with and without hypertension, and with and without papillary

necrosis. The results of this series of studies have been reported in the articles listed below. These constitute the basis for the following survey and discussion. The articles will be referred to by the respective Roman numerals.

- I Arne Ljungqvist and Curt Lagergren: Normal intrarenal arterial pattern in adult and ageing human kidney. A micro-angiographical and histological study. *J Anat.*, 96:285—300 1962.
- II Arne Ljungqvist: Fetal and postnatal development of the intrarenal arterial pattern in man. A micro-angiographic and histologic study. *Acta paediat.*, 52: 443—464 1963.
- III Arne Ljungqvist: The intrarenal arterial pattern in essential hypertension. A micro-angiographic and histological study. *J Path. Bact.*, 84: 313—325 1962.
- IV Curt Lagergren and Arne Ljungqvist: The intrarenal arterial pattern in chronic pyelonephritis. A micro-angiographic study. *Virchows A* 335: 584—597 1962.
- V Curt Lagergren and Arne Ljungqvist: The intrarenal arterial pattern in renal papillary necrosis. A micro-angiographic study. *Amer J P* 643 1962.



arterial tree Virchow (71) treated the kidney tissue chemically to render it transparent — a process known as clearing. He paid particular attention to the vascular supply of the medulla in one case of amyloidosis and found that this consisted partly of aglomerular arterioles (*arteriolae rectae verae*).

Since the clearing technique was improved by Spalteholz (64) it has been applied in a large number of studies to examine the stereoscopic appearance of the intrarenal arterial pattern. MacCallum (51-52) evolved a method for selective staining of artery and vein walls and studied in animals the effect of changes in the glomeruli on the appearance of the intrarenal arterial pattern. He reported that the afferent and efferent arterioles of degenerated juxtaglomerular glomeruli formed aglomerular vessels that passed through the glomerular scars, and thus formed *arteriolae rectae verae* leading to the medulla. Using the same method on human kidneys Moore (56) could not find MacCallum's *arteriolae rectae verae*. Hou-Jensen (37) found a small number of aglomerular arterioles both in the cortex and in the juxtaglomerular zone of kidneys from fetuses and adults. Gänsslen (24) recognized such arterioles not only in the normal kidney but in a number he supposed were diseased. Spanner (65) described arteriovenous anastomoses in the human kidney but Staubesand & Hammersen (66) could not confirm this finding and considered that the anastomoses reported by earlier authors were artefacts. Hammersen & Staubesand (31-32) also studied the vascular supply of the ar-

teriole region and the renal capsule in man and reported that in these regions blood might reach the venous side without first passing through glomeruli. Using laboratory animals, Lewis (45-46) examined the development of the vascular system in the metanephros, and the structure of the glomerular capillary tuft.

### *Corrosion cast method*

The corrosion cast technique was used by a number of research workers in the 1800s for studying the anatomy of the intrarenal arterial tree (for references see Hou-Jensen). The injection media in use at that time were, however not sufficiently plastic in the hardened state for an accurate manipulation of the finer arteries to be possible. Huber (38) and Morison (58) performed such studies on celloidin casts. Examining a series of laboratory animals Huber found *arteriolae rectae verae* in the dog. He was the first to voice the opinion that such vessels might be the result of degeneration of corresponding glomerular capillary tufts. His view was supported by the findings of Morison who made similar observations on man.

During the last two decades or so improved injection materials have become available and as a result the corrosion cast technique has come into more common use. In neoprene casts Shonyo & Mann (63) found occasional *arteriolae rectae verae* in normal kidneys from laboratory animals, and they reported the presence of constrictions at the glomerular end of afferent arterioles in cases of experimental hypertension.

Trueta, Barclay Daniel, Franklin & Prichard (70) found on similar casts that the juxtamedullary arterioles were numerous and wide enough to carry all the intrarenal blood over the medulla, with resulting ischaemia of the cortex. They had already observed such a disturbance of the intrarenal circulation in angiograms recorded on experimental animals under various conditions. These authors also supported the view that the arteriole rectae verae resulted from degeneration of the glomeruli. More & Duff (57), who studied neoprene casts of the human renal arterial tree, agreed that the juxtamedullary arteriole-glomerular units had a large enough capacity to carry all the intrarenal blood by way of the medulla. Arteriole rectae verae could not, however be found in appreciable numbers in normal kidneys but they were more numerous in one hypertensive kidney.

Using the corrosion technique, Trabucco & Márquez (69) studied the passage of the postglomerular cortical vessels into the venous system. They found that some efferent arterioles emptied into veins without first forming capillaries. On casts of dog kidneys Costa, Carvalho & Rangel (16) found fine interglomerular anastomoses. Examining kidneys from premature and full term fetuses, Montagnani & Carrai (55) found no notable deviation from the corrosion specimens of the adult kidney. Zlábek (75) studied in particular the glomerular capillary tuft in different parts of the cortex of the human kidney and noted that the juxtamedullary unlike the cortical, glomeruli had an anastomosis be-

tween the afferent and efferent arterioles at the vascular pole.

In experimental animals Tagarrello & Dòmini (67) found a constriction at the site of origin of the afferent arterioles this had also been observed in the human kidney by Morison and More & Duff. Analysing these constrictions more closely Dòmini (19) reached the conclusion that they probably represented a mechanism for regulating the circulation through the arterioles.

In a study of the blood supply of the renal papillae Baker (1) found that at least part occurred via vessels from the arterial system of the renal pelvis. Von Kügelgen, Kuhlo, Kuhlo & Otto (42) reported their observations on both arterial and venous corrosion casts of the dog kidney in a monograph. They found no arteriole rectae verae of the medulla or aglomerular cortical arterioles, nor did they observe any definite arteriovenous anastomoses. In corrosion casts Gömöri Munkácsi, Szalay Tu Süj-Haj & Zolnai (28) and Gömöri, Szalay Tu Süj-Haj & Zolnai (29) found an increase in the number of arteriole rectae verae in chronic renal insufficiency in man and laboratory animals.

### *Angiographic method*

Owing mainly to the limited resolution of the regular X-ray film the angiographic technique has in the past been used only for the vessels of fairly wide calibre. Even on enlarged angiograms Graham (27) was unable to study the finer branches in normal and diseased kidneys.

To enable the finer vascular segments to be explored by a radiologic technique high resolution X ray film has been developed during the last few decades. Bohatyrtachuk (10) prepared such films himself and demonstrated capillary vessels in human organs injected with thorotrast. Barclay (2) developed this micro-arteriographic technique and recorded his experience in a monograph published posthumously. The possibilities of the method are surveyed, including the production of micro-arteriograms of the kidney which are only briefly discussed.

In Sweden, Bellman (5) made a closer analysis of the technique. In particular he examined the factors that determine the quality of the radiograph, such as the size of the X ray focus, the grain size of the film, the type of contrast medium and the geometric requirements for the radiographs to reproduce correctly the angioarchitecture of the specimen under examination. He referred to the technique as micro-angiography. A term that has since gained general currency he stressed the value of the stereoscopic technique, which he demonstrated on for instance, micro-angiograms of the kidney. An analysis of these did not come within the scope of his study however.

The micro-angiographic technique has since been used in many scientific investigations, but few have been concerned with the intrarenal vascular anatomy and then they have been restricted to particular problems. For instance Bellman & Engfeldt (6) included the micro-angiographic technique in a study of the

structural changes in the kidney in experimental hypervitaminosis D. By means of micro-angiography Ivemark & Lindblom (39) studied the relation between intrarenal vessels and cysts in the adult polycystic kidney and Ivemark, Ljungqvist & Barry (40) the renal changes in Fanconi's juvenile nephronophthisis. With the aid of renal micro-angiograms, Burghelle & Rugendorff (14) evaluated the functional status of the vessels of persons dying from shock. In the United States the micro-angiographic technique has been demonstrated on kidney specimens by Chang & Tremblay (15), though no analysis of the angiograms was performed.

#### *Microdissection method*

In this technique a tissue is macerated in, for instance, concentrated hydrochloric acid, after which various structures can be dissected under the stereomicroscope. Experience of a series of such studies of the vascular and tubular architecture of the kidney in Bright's disease has been reported by Oliver (59). Many glomerular arterioles were observed, those in the cortex forming capillaries and those in the juxtamedullary zone forming arterioles rectae leading to the medulla. Tissue from a normal human kidney was examined by microdissection by Bualetstock (9). She, too observed glomerular arterioles in the cortex and in the juxtamedullary zone and found evidence that an efferent arteriole supplied the tubules not only of its glomerulus but of adjacent ones.



## Discussion

The studies performed by time-consuming serial sectioning and reconstruction have for technical reason been restricted to extremely small segments of vessels, such as individual glomeruli and arterioles. Consequently no complete picture of the intrarenal arterial pattern could be obtained. The studies in which selective staining of cybroscics was used could only include evaluation of the vessels, since the other structures had to remain unaltered; moreover the appearance of the vessel specimen was determined by the blood distribution in the kidney which cannot be taken for granted to represent the actual vascular anatomy.

As is evident from the above survey of the literature, the intrarenal arterial pattern has been studied almost exclusively by the stain injection and clearing technique and by the corrosion cast and microdissection methods. The results have been to some extent contradictory probably owing to the variety of methods applied and species examined. In none of the studies performed by these methods was a parallel histologic examination of the specimens performed. Consequently no check could be made of the extent of filling of the injection specimens, and it cannot be ruled out that filling defects observed were artefacts simply due to incomplete filling of the arterial tree. Nor could it be certain that structures judged to be vessels were not in fact artefacts, resulting from rupture of the vessels. In addition

the positional relationship between the vessels and the other tissue components could not be assessed.

By their very nature the corrosion cast and microdissection methods do not permit of a parallel histologic examination of the specimens. The same seems to be true of the stain injection and clearing method, at least until 1964 when Zinser & Rosenbauer (74) claimed to have evolved a procedure for combining this technique with histologic examination. However Hinman, Morrison & Lee-Brown (34) who compared the stain injection — clearing, corrosion cast and angiographic methods state: "The barium sulphate roentgenographic study of circulatory arrangements and changes is ideal when preservation of the pathologic or anatomic specimen and subsequent histologic study is desired. As regards the kidney a subsequent histologic examination is always desirable, since the grossly normal kidney often displays changes (61). This has also been pointed out by Fishberg (2).

It cannot be too strongly emphasized that the kidney should not be pronounced uninjured purely on the basis of the naked eye findings without the confirmation of microscopic examination.

Thus the most suitable method of those available to-day for studying the intrarenal arterial pattern in the normal and diseased kidney is a combination of micro-angiographic and histologic examinations of the same. Such study has been reviewed in the literature.

## Summary

The fine intrarenal arterial pattern has previously been studied by reconstruction of individual vessels from serial sections, selective staining of the erythrocytes in sections, various injection methods involving clearing or corrosion of the rest of the tissue or by microdissection.

The findings have been contradictory especially as regards the presence of glomerular arterioles in the normal kidney. On the whole, no reliable investigations of the arterial pattern of pathologic kidneys have been performed. The reason for the prevailing uncertainty relating to the arterial pattern of the normal and diseased kidney lies in the short-comings of the methods of investigation used hitherto.

The reconstruction method is too time-consuming to be of practical use in the study of the arborization of the intrarenal arterial tree. With the erythrocyte-staining method the other tissue

components remain unstained and the relation of the vessels to these is therefore difficult to judge. Moreover the appearance of the vascular tree is dependent on the distribution of the blood in the kidney. On the other hand, the various injection methods, in common with the microdissection technique, have not included the histologic examination of the specimens essential to the unambiguous evaluation of the findings in both normal and diseased kidneys.

The micro-angiographic method is superior to those used earlier since it permits of both stereoscopic examination of the arterial tree in a kidney and histologic study of the same specimen. Thus enables the extent of filling and the histologic status of the specimens to be verified. In addition, the course of the vessels among the other tissue components can be explored.

No systematic micro-angiographic studies of the sound and diseased human kidney has been reported hitherto

## Material and Methods

The study was performed on 183 kidneys. 135 of these were grossly and histologically normal for their age and were obtained from 92 subjects, the smallest a fetus from the end of the third fetal month (II) and the oldest a 79 year-old patient (I). The various stages of development from the fourth fetal month to the twentieth year of life were fairly uniformly represented in the material (II). Thereafter the age distribution was also even, with 3—6 of the kidneys from each decade up to the eighth. Of the 135 kidneys, 133 were from autopsies and the 2 others had been removed on extra renal indications. These two organs displayed no signs of pyelonephritis or hydronephrosis.

Eighteen other autopsy kidneys were obtained from cases of essential hypertension, 15 of whom had a benign and 3 a malignant symptom picture (III).

The other 30 specimens consisted of 15 from cases of chronic pyelonephritis without renal papillary necrosis (IV) and 15 from 13 such cases with papillary necrosis (V). Of the former and latter groups, respectively 8 and 9 of the kidneys were surgical specimens. The other kidneys were obtained at autopsies.

The autopsies on children and adults were usually performed 1—3 days after death, during which period the bodies had been kept at about  $+4^{\circ}\text{C}$ . Many of the fetal kidneys were taken only 4—6 hours after birth or death, others from fetuses that had been preserved at

about  $-20^{\circ}\text{C}$ , for periods of up to 5 years. The kidneys, extrarenal arteries and the lumbar aorta were removed *en bloc* care being taken to avoid lesions to the kidney vessels and capsule so as to diminish the risk of leakage of the contrast medium to be injected subsequently. The medium used was a fine 7.5 per cent aqueous suspension of barium sulphate (Micropaque). When the suspension had sedimented for 5 hours to separate the largest particles it was bottled and left to stand a further 48 hours before use.

The suspension was injected into the renal arterial tree *via* the aortic orifice of the renal artery (the larger fetuses, children and adults) aorta (the smaller fetuses) or *via* the extrarenal arteries (the surgical specimens). To enable a continuous recording to be made of the injection pressure and, when required, of the amount of contrast medium injected, a simple apparatus was designed (Fig. 1). Preliminary test injections showed that the best filling of the vascular tree was obtained if the injection pressure was kept fairly low at first, and then raised slowly over a period of hours. For the fetal kidneys an initial pressure of 10—20 mm Hg and a terminal pressure of 60—80 mm were found to be suitable. The corresponding values for the children's kidneys were 20—40 and 80—120 mm, and for the adult organs 60—80 and 150—200 mm. At higher

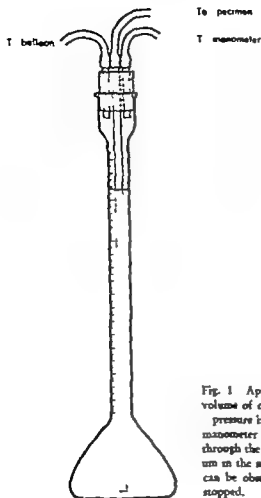


Fig. 1 Apparatus for recording the injection pressure and volume of contrast medium injected. By pumping the balloon, pressure is set up in the flask, which can be recorded on the manometer scale, and which will force contrast medium up through the middle tube. By maintaining the level of the medium in the narrow graduated neck of the flask, the slow flow can be observed that indicates when the injection should be stopped.

pressures rupture of the vessels was common.

The preliminary injection tests showed that the medium at first flowed into the arterial tree of the kidney at a fairly rapid rate, but after 20 minutes or so the flow retarded and after a further 2—3 hours became constant at a very low level. If the level of the medium in the flask was now kept with in the narrow graduated neck it was

found that it fell very slowly and continued to do so at an approximately constant rate for a further 6—8 hours. No injections of longer duration were performed. Micro-angiographic and histologic examinations of the injection specimens showed that if the injection was discontinued after the first rapid phase of filling, that is, after about 20 minutes, the filling was usually incomplete and the medium had not reached

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Fig. 2. This figure illustrates the parallel study of the micro-angiogram and the serial histologic sections of the same specimen.

A. Micro-angiogram from the postmedullary zone showing an arcuate artery (larger arrow), number of glomerular arterioles (smaller arrows), an afferent arteriole leading to glomerular tuft (bottom) and fairly complete capillary filling. The glomerular arterioles course more or less parallel to the arcuate artery before turning off almost at right angles into the medulla to form arterioles rectae (left). The lower two smaller arrows indicate irregular protrusions from the arterioles.  $\times 100$ .

B. This picture of one of the serial histologic sections corresponds to the top half of Fig. A. It shows the arcuate artery (larger arrow) and the three glomerular arterioles (smaller arrows).

The irregular protrusion from the arteriole at the arrow second from top in Fig. A is seen to consist of still patent capillaries of cystically degenerated glomerulus (bottom smaller arrow). This is traversed by the arteriole. The arteriole at the top arrow in Fig. A is seen to pass through scarred glomerulus (top arrow), no evidence of which is seen in Fig. A. Alcian blue-PAS  $\times 100$ .

C. This picture of another of the serial histologic sections corresponds to the bottom half of Fig. A. It shows the arcuate artery (larger arrow) and the third of the glomerular arterioles. This is seen to pass through cystically degenerated glomerulus (smaller arrow), still patent capillaries of which correspond to the irregular protrusions at bottom arrow in Fig. A. van Gieson.  $\times 100$ .

kidneys were embedded either whole or after dividing frontally

In the micro-angiographic procedure a Marchlett OEG 50 X ray tube was used. The exposure was made at 40 kV

and 8 mA on Kodak Maximum Resolution Plates (resolution better than 1000 lines/mm). To obtain an acceptable depth of focus even of the thickest blocks the film-to-focus distance was made

riety of the tissue was the reason for the tendency for vascular rupture in the fetal kidneys, the resistance to the injection pressure then being low

While the injection may thus result in distension and rupture of the vessels, in other cases it may provide extremely incomplete filling of the vascular tree, even if the injection technique itself is sound. In fact, complete filling of the vascular tree of the organ could not be obtained, the experience of practically all workers concerned with injection studies. Nor would complete filling be desirable, since the capillary network would then overshadow the other vascular structures. The essential point is that it should be possible to determine the degree to which the specimen is filled, for only then can it be decided whether filling defects in the individual vessel and the vascular pattern as a whole are due to structural changes or whether they are artefacts resulting from incomplete filling. This object can be achieved by micro-angiography followed by histologic examination of the radiographed specimen.

The preparation of the kidneys involves a risk of deforming the specimen and hence its vascular pattern. Since the pathologic and normal kidneys were prepared in the same manner differences in their vascular patterns would be expected to provide significant information. It cannot be ruled out, however, that pathologic and normal kidneys may be affected to different extents by the technical procedures. Hence, in general it is the variations in the micro-angiographic pattern with a demonstrable

structural basis that are likely to be of greatest significance. This further underlines the importance of performing a histologic examination of the tissue the vascular supply of which has been studied by the injection technique.

The micro-angiographic technique should be so designed as to provide a correct picture of the specimen. The requirements for this have been analysed by Bellman (5). The method for the present investigation was developed on the principles laid down by him and the stereoscopic technique was used to avoid confusing overlapping phenomena. The radiographs constituted a full-scale picture of the specimen, since this was in contact with the film and the thickness of the specimen was negligible compared with the focus-to-film distance. For the same reason any irregularities in the thickness of the specimen and patchy irregular contact between this and the film may be disregarded. The technique may however give rise to stereoscopic aberrations with consequent inaccuracies in measurements performed on the micro-angiograms. To enable correct measurements to be made, it must be possible to work with standardized conditions with respect to the focus-to-object and object-to-film distances and the length of the base line (the distance between the corresponding points in the specimen at the two exposures). Since no measurements of structures reproduced in the micro-angiograms were to be made in these studies, no such exact determinations were performed, the stereo technique being used simply to "separate" vessels from one another and to obtain

an impression of their spatial course in the renal tissue. It was then also easier in the histologic sections to follow the vessels studied in the micro-angiograms.

Preparation of the kidneys for histologic examination involved a number of departures from the usual procedure. For instance they had first been injected with contrast medium and prepared in a special manner for micro-angiography before they were embedded as blocks, radiographed and sectioned for histologic examination. This sequence of procedures might be thought to result in deviations from the histologic picture presented by the kidney sections prepared by the routine methods. The observed differences between the micro-angiographed and the contralateral non-injected kidneys from autopsies could all be ascribed to the injection, the other procedures apparently not affecting the histologic picture. For instance, the vessels were filled with contrast granules, by which they were obviously distended, and this gave them a circular cross-section and a considerably wider lumen in relation to the wall thickness than is usually seen in the ordinary histologic

section. This had to be borne in mind in the evaluation of the extent of the wall thickening in the pathologic kidneys. Moreover the interstitial tissue displayed some degree of oedema. It is probable that water in the contrast suspension flowed through the vessels and out into the tissues, leaving only the granules of the medium in the lumen. Even when the vessels were completely filled with granules the water probably continued to flow and to cause interstitial oedema. Evidence that this was the case is found in the fact that even after the vessels, as judged by the histologic examination, were filled with medium, the level in the flask of the injection apparatus continued to fall slowly without there being any improvement in the filling. The changes in the histologic picture due to the injection in no case led to difficulty in the histo-pathologic diagnosis.

Re-embedding and sectioning of the radiographed blocks often resulted in a slight shrinkage of the histologic sections, so that they were smaller than the corresponding micro-angiograms. This, however did not complicate the tracing of vessels in the histologic sections.

## Summary

Micro-angiographic and histologic techniques were applied in a study of the intrarenal arterial pattern in normal human kidneys from the fourth fetal month to the 79th year and in kidneys from cases of essential hypertension, chronic pyelonephritis and renal papillary necrosis.

The composition of the material is analysed and judged to be representative.

The methods of investigation are described and the changes that these might produce in the anatomy of the intrarenal arterial tree are discussed. Account is taken of (i) essential deviations in the



micro-angiographic pattern of kidneys removed from the body from the vascular pattern in the kidney *in situ* (ii) changes in the micro-angiographic pattern that may be due to the treatment of the specimens, (iii) the extent to

which the micro-angiograms correspond to the vascular pattern of the radiographed specimens, and (iv) the changes in the histologic vascular pattern that may be due to the treatment of the specimens.

/

## Survey of Findings

### 1 *The normal pattern in the adult and ageing kidney*

This series consisted of kidneys from subjects with ages ranging from 20 to 79 years. In the micro-angiograms of the younger kidneys the interlobar arteries in the region of the renal pelvis branched to form arcuate arteries that coursed along the corticomedullary junction, from the pelvic ends of the renal columns and into the renal lobes. After running for various distances they turned off into the pyramidal cortex as interlobular arteries. As they passed along the corticomedullary junction the arcuate arteries also gave off interlobular vessels into the renal columns and the pyramidal cortex. The interlobular arteries followed a straight course and gradually narrowed they gave off several afferent glomerular arterioles and a few individual vessels having the course and calibre of afferent arterioles but either splitting up into a few fine capillaries or ending blindly.

In addition to the interlobular arteries the arcuate vessels gave off afferent arterioles, which coursed for long distances along the medullary side of the arcuate arteries before forming glomerular tufts. These glomeruli, and some belonging to the afferent arterioles leaving the extreme proximal segment of the interlobular arteries, gave off wide efferent arterioles, which split up into bundles of arterioles rectae spuriae.

These coursed into the medulla where arterioles were seen to leave some bundles to link up with adjacent ones. A few arterioles rectae were of the verae type in that they were branches from an arteriole that had no glomerular tuft. Other arterioles that formed arterioles rectae carried what appeared to be a glomerular tuft, consisting of a few fine and short capillaries somewhere along their course. Further in the cortex the efferent arterioles were considerably thinner than in the juxtamedullary region and they split up after a short distance into small capillaries which formed anastomosing networks around the tubules. These arteriole-glomerular units are referred to as cortical, those forming arterioles rectae as juxtamedullary. The afferent arterioles, and particularly those given off by the arcuate arteries, were often constricted at their site of origin from the parent vessel.

Histologic examination showed that the cortical arterioles that were apparently aglomerular and directly formed small capillaries, were in fact atrophied afferent arterioles the small capillaries were parent vessels in the degeneratively changed glomerulus. The arterioles that ended blindly were found to terminate in, or near the vascular pole of totally degenerated glomeruli. The juxtamedullary arterioles that formed arterioles rectae after having given off a few small glomerulus-like capillaries, or that showed no evidence of a tuft, passed

through, or tangentially to, partly or completely degenerated glomeruli. However along some of the aglomerular arterioles that coursed for long distances within the perivascular connective tissue on the medullary side of the arcuate arteries, no definite glomerular scars could be identified. The constriction of an afferent arteriole at its site of origin occurred at the segment that passed through the wall of the parent vessel.

The older the kidney the greater the number of aglomerular arterioles observed. The cortical ones terminated blindly near degenerated glomeruli, the juxtamedullary ones passed through such glomeruli and formed arteriole rectae verae. In the histologic sections the number of degeneratively changed glomeruli thus increased with age, as did, to some extent, the interstitial connective tissue. In addition to the rise in the number of aglomerular arterioles with age there was an intensification in the spiralling of the afferent arterioles and the distal segment of the interlobular arteries, but not of the efferent arterioles or the wider branches such as arcuate and interlobar arteries.

## II *The pattern in the fetal and postnatal kidney*

In this study the development of the arterial pattern of the metanephros was studied from about the beginning of the fourth fetal month to 20 years. In the youngest of these kidneys there were well developed glomeruli near the cavity of the renal pelvis these had afferent arterioles and evidence of efferent ones.

Towards the end of the fourth fetal month there was a corticomedullary differentiation of the vascular pattern this then showed obvious interlobular arteries, a cortical arrangement of glomeruli, and efferent arterioles in the juxta medullary zone, which gave rise to arteriole rectae of the medulla. On the other hand, no postglomerular vessels were observed in the cortex. Many glomeruli were localised in the connective tissue of the renal pelvis. Their afferent arterioles were given off by wide branches in the area, as a rule the efferent arteriole coursed to the nearest calyceal recess, over which it turned down into the medulla as a bundle of arteriole rectae. From the afferent arterioles of these arteriole-glomerular units branches were given off to the connective tissue of the renal pelvis. During the sixth fetal month degenerative changes appeared in glomeruli located in the pelvic and periarculate connective tissue. At 6 months of age all the pelvic and many of the periarculate glomeruli had completely degenerated, but their arterioles ran unchanged through the scarred glomeruli to form arteriole rectae. The glomerular scars were gradually incorporated into the connective tissue and became histologically unidentifiable. The vessels from the pelvic afferent arterioles divided progressively during fetal life into branches that to some extent assumed a spiral course and anastomosed with similar branches from other such arterioles.

Not until the end of the eighth fetal month did efferent arterioles also appear in the cortex, and these split up into

peritubular capillaries. About this time degenerative changes were also seen in the cortical glomeruli, with atrophy of the whole arteriole-glomerular unit. At 7 years of age degenerative changes also appeared in juxtamedullary glomeruli outside the periarculate connective tissue. Here scarred glomeruli were traversed by their arterioles, which formed arterioles rectae verae.

### III. *The pattern in essential hypertension*

In kidneys from cases of clinically benign hypertension and histologically benign nephrosclerosis there was an abnormally high number of glomerular arterioles for the age. The juxtamedullary glomerular arterioles passed through their respective glomerular scars and formed arterioles rectae, while the cortical ones were atrophied and ended blindly near their scars. In addition both the afferent arterioles and the interlobular arteries were spiralled, kinked and irregular in calibre. The vessel wall displayed patchy sclerosis, varying in degree from one part of the vessel wall to another. Micro-angiographic changes in calibre could as a rule not be ascribed to this focal sclerosis although the constriction at the site of origin of an afferent arteriole corresponded to the segment of the arteriole that passed through the sclerotic wall of the parent artery.

In some kidneys the changes described were marked, in others mild. The material was divided into 3 groups according to degree — mild, moderate and severe changes. In kidneys with moderate and

severe changes the postglomerular cortical vessels were wider than normally and a few veins contained contrast medium. The afferent arterioles with intact glomeruli were as a rule considerably dilated at their intraglomerular segment, though this feature was not definitely related to the severity of the aforementioned changes. The efferent segment of the glomerular juxtamedullary arteriole displayed hyalinosis of the wall, unlike the efferent arterioles from intact glomeruli.

In kidneys from cases of clinically malignant hypertension and histologically malignant nephrosclerosis the changes were largely similar to those described above. However there was a more marked reduction in the vascularization of the cortex, with obliteration of interlobular arteries and arterioles. Moreover the parent postglomerular vessels in the cortex were considerably wider than was the case in benign hypertension, and they displayed irregular winding courses.

### IV. *The pattern of chronic pyelonephritis*

In inflamed regions a number of cortical and juxtamedullary glomeruli were devoid of postglomerular vessels. In the cortex there were also atrophic afferent arterioles that terminated blindly near glomerular scars. In some kidneys, whether hypertensive or not, the walls of the cortical vessels in the inflamed areas were greatly thickened, while in other kidneys from both hypertensive and normotensive subjects such changes

were mild or absent. In all the kidneys inflamed areas in the juxtamedullary zone contained arterioles that passed through glomerular scars and formed arterioles rectae. In a few cases the cortex, too, displayed areas in which arterioles were observed to pass through glomerular scars to form anastomosing networks. The tissue in these areas displayed thyroid-like changes.

Periglomerular fibrosis was a typical feature, and was most marked around the vascular pole, especially in the glomeruli that were devoid of postglomerular vessels.

In 2 of the kidneys a few medullary pyramids contained small circumscribed areas of necrosis. These were approached by bundles of arterioles rectae composed of normal and intensely spiralled, wide and thick walled arterioles.

#### V *The pattern in renal papillary necrosis*

In all the kidneys displaying papillary necrosis there was also chronic pyelonephritis with vascular and histologic changes of the aforementioned types. In addition, various stages of the pathologic papillary process were seen as a rule, however these were at about the same stage in all the medullary pyramids of a particular kidney. In some kidneys the

papillary necrosis seemed to be quite fresh, while in others the necrosis was obviously older with evidence of organization at the borders. In some kidneys the necrotic papillae were sloughed and the excavated surface of the medulla showed signs of re-epithelialization, with sclerosis of the adjacent medullary tissue.

Medullary pyramids with fresh necrosis were supplied by bundles of arterioles consisting of both normal and wide intensely spiralled arterioles rectae with thick walls. Such pathologic arterioles were also seen in pyramids with intact papillae.

Also medullary pyramids with evidence of organization at the borders of the necrotic areas were supplied by bundles of arterioles rectae, which contained changed vessels. These were, however narrower and less intensely spiralled than where the necrosis was more recent. There were no signs of vascularization of the necrotic areas but at their borders there was a dense network of capillaries.

In the medullary pyramids with sloughed papillae there were pathologic arterioles, which were only slightly wider than the others, and only mildly spiralled. Beneath the excavated surface of the medulla there was a fairly sparse capillary network in the sclerotic tissue.

## Discussion of Findings

### Spiralling of the vessels

In all the materials spiralling vessels were observed this feature might be ascribed to deformation of the specimens and the vessels during fixation and the subsequent preparation or to a selective effect on the vessels during injection. In such cases spiralling would be evident in all the kidneys and all the vessels, but in fact only those of the renal pelvis were spiralled in kidneys from fetuses and younger subjects although these were prepared by the same method as the other kidneys that displayed spiralling also in other areas. In these areas, as in the renal pelvis, the spiralled vessels alternated with straight ones—further evidence that the spiralling was no artefact. Thus, in normal kidneys from elderly persons and in kidneys from hypertensive subjects the changes were more severe in pre- than postglomerular vessels. In the pyelonephritic kidneys from normotensive subjects the most intensely spiralling vessels occurred in the inflamed areas, and in the kidneys displaying papillary necrosis spiralling and straight medullary arterioles ran side by side. There is thus a convincing body of evidence that the spiralling of the vessels is an intravital feature. On the cause and importance of these changes in the different cases purely morphologic examinations of injection specimens are not very

informative, but the following points may be considered.

*Spiralling vessels in the normal kidney* — That the wall of the renal pelvis normally contains spiralling vessels is a well-established fact, and the significance of their presence has been tentatively analysed. Thus, Douville & Hollinshead (20) considered that the spiral form was a device to enable the vessels to be stretched by distension of the renal pelvis without risk of rupture, but this is hardly likely in view of the fact that many pelvic vessels are straight (30 1). Moreover Hamner & Staube sand (30) found that the spiralling was not eliminated even by powerful distension of the pelvic cavity. They saw the spiralling chiefly as a mechanism for regulating the blood flow especially through the vessels given off by the pelvic arteries to enter the medullary pyramids. This view is probably unjustified since it has been found that the medullary vessels intended by Hamner sen & Staube sand (31) leave the interlobar arteries of the pelvic region and develop vessels to the pelvic wall as side branches (11). It is difficult to suggest an alternative effect of the pelvic spiralling vessels on the intrarenal haemodynamics since, as mentioned above, conclusions can hardly be drawn on the basis of the injection studies. All that can be said for certain is that spiralling pelvic arteries occur normally in man, that they develop as originally straight

or slightly winding branches from pelvic afferent arterioles, and that during fetal life they start to spiral and anastomose with similar vessels from other arterioles.

Apart from the renal pelvis, spiralling arteries in normal kidneys were encountered only in the cortex and then only in specimens from elderly subjects. This type of spiralling had the same characteristics as that observed in the cortex of hypertensive and pyelonephritic kidneys, and will therefore be discussed in connection with these under the heading "spiralling vessels in the diseased kidney".

*Spiralling vessels in the diseased kidney* — It is a familiar fact that newly formed vessels may follow a tortuous or spiralling course, for instance in granulation tissue. It has also been shown that originally normal and straight vessels may develop spiralling. Gänsslen (24) observed this feature in what he supposed to be pathologic kidneys and considered that this was due either to a shortening of the vessels caused by fibrotic contraction of the surrounding tissues or to an elongation of them, the end-points remaining stationary. In an experimental investigation on the intestinal mesentery of the rat Werranch & DeGaris (73) demonstrated that such an elongation and spiralling of the vessels with dilatation of their lumen and thickening of their walls occurs if adjacent vessels leading to the same peripheral vascular bed are ligated. The feature may thus constitute a collateral vascular response, and in experiments on arterial anastomosis fistulas Holman (36) found it to be due to the vessels linking

vascular beds of different pressures. Bellman, Frank, Lambert & Roy (7) showed that microscopic vessels, too dilate and assume a spiralling course in collateral adaptation.

The spiralling of medullary arterioles observed in kidneys with papillary necrosis (V) probably represented a collateral adaptation. It has been shown that a bundle of arterioles rectae consists of vessels from various juxtamedullary arterioles (70 I) and damage to some of these would be expected to elicit collateral adaptation of arterioles rectae arising from undamaged ones. In the kidneys with papillary necrosis some juxta medullary glomeruli had no efferent arterioles and there was evidence that this was due to constriction of these thin-walled vessels by the periglomerular fibrosis, particularly marked around the vascular pole, or to compression of the arterioles by the inflammatory exudate in the juxtamedullary zone. On the other hand, the spiralling could not be ascribed to any fibrotic contraction of the surrounding tissue, nor could it have been secondary to the necrosis, since spiralling arterioles were seen also in medullary pyramids with intact papillae.

Spiralling periglomerular vessels were observed in the cortex of pyelonephritic and hypertensive kidneys and in normal kidneys from elderly subjects. These vessels occurred in tissue with evidence of fibrotic contraction and this may be one cause of the spiralling. This assumption is supported to some extent by the fact that the spiralling was more intense the more severe the fibrosis, and thus

most intense in the pyelonephritic scars. However the spiralling was not so marked in post as in preglomerular vessels, a fact that suggests that it was not due solely to the contraction, since all the vessels in the tissue would then have been affected to about the same degree. The observed degeneration and atrophy of some cortical arteriole-glomerular units may on the other hand, have created a situation that would induce collateral adaptation of still patent units. It might be thought that in this mechanism, too, the pre- and postglomerular vessels would be affected to the same extent, but since collateral adaptation is a response to an increase in the pressure gradient along the vessels (36) it is conceivable that the presence of a capillary tuft between the pre and postglomerular vessels would modify the reaction, for instance by a change in the glomerular filtration.

### Constriction of the afferent arterioles

Though the constrictions at the origin of the afferent arterioles have been observed in several earlier injection studies and have been ascribed importance in the regulation of the blood flow through the arterioles (19-58), their relationship to the adjacent structures has not been considered owing to the absence of comparative histologic studies. The present studies (I-III) have revealed that the constriction occurs in the segment of the arteriole passing through the wall of the parent artery. That they are similar to the constrictions observed by earlier workers is evident

from their illustrations and from the fact that in all investigations the constrictions were most pronounced in the arterioles given off by the larger vessels, such as the arcuate arteries. It cannot be ruled out that the constrictions actually represent a functional regulatory mechanism, as was supposed by the earlier workers. Nor however can it be excluded that they are artefacts due to a greater resistance of this initial segment to the injection pressure than of the rest of the arteriole the wall of which therefore yields. The more marked constriction in the nephrosclerotic kidneys would then be due to the greater rigidity of the sclerotic wall of the parent artery. It is in fact impossible on the basis of purely morphologic studies of injection specimens to decide whether the constrictions are intravital phenomena with a functional significance, or whether they are artefacts caused by the injection. This is a problem that might well be solved by study of the vascular anatomy of living tissue available for micro-angiography—studies of the type performed by Bellman *et al.* (7) on the rabbit ear for instance.

### Aglomerular arterioles

The investigation, in common with those performed earlier by for instance Traetz *et al.* (70), has shown that whereas the cortical arteriole-glomerular unit consists of a wide afferent arteriole, a glomerular capillary tuft and a thin efferent arteriole that splits up to form peritubular capillaries, the juxtamedullary unit has an afferent and efferent



arteriole of roughly equal width, the latter splitting up into arteriolae rectae (spuriae) leading to the medulla.

In all the materials (I V) aglomerular arterioles were also observed, the cortical one terminating in or near a degenerated glomerulus, the juxtamedullary one passing through its degenerated glomerulus and continuing, with calibre unchanged, into the efferent arteriole, which split up into arteriolae rectae (verae) leading to the medulla. In addition there were aglomerular medullary arterioles deriving from the renal pelvis. The study of the fetal kidneys (II) showed that these were formed through the degeneration of glomeruli situated in the pelvic connective tissue. Even in the fetal stage, however both cortical and juxtamedullary aglomerular arterioles were found, and after birth they increased in number with age they were still more common in kidneys from cases of hypertension and pyelonephritis. A purely mathematical determination of the occurrence of aglomerular arterioles for different ages and conditions would be the most rewarding. Such a calculation was not performed, however since because not all the vessels were filled, it would not have yielded accurate values. Moreover the difference in frequency of aglomerular arterioles under varied conditions was obvious, as these vessels were formed through degeneration of glomeruli, which is known to become more extensive with age (60) and in renal disease.

*Cortical aglomerular arterioles* — Opinions diverge on the presence of aglomerular arterioles in the cortex of

the normal kidney. It has often been maintained that there are none (11 38 56 57 70 71) while those who accept their existence consider that they form peritubular capillaries directly (9 17 24 37 44 50 63). In the present investigation no such capillary forming vessels were found in the cortex, whether in the normal or the pathologic kidney the aglomerular cortical arterioles that did occur ended blindly in or near glomerular scars. It is probable that vessels with this appearance represent a transitional stage of a process of degeneration terminating in complete atrophy of the glomerulus and its associated vessels. Evidence of this terminal stage was recognized at least in the fetal kidneys, the afferent arteriole of some degenerated glomeruli being converted to a fibrous strand.

The micro-angiograms often gave the impression that the aglomerular cortical arterioles did form peritubular capillaries. However histologic examination proved these to be either still patent capillaries in partially degenerated glomeruli, or peritubular capillaries belonging to efferent glomerular arterioles that were not recognizable from the micro-angiograms alone. Thus, even with the stereo-micro-angiographic method of examination it was often difficult to separate such small vessels as efferent arterioles and capillaries. It is highly probable that the cortical arterioles described by previous authors as forming peritubular capillaries directly either consisted of partially degenerated arteriole-glomerular units with some patent glomerular capillaries, or constituted an

overlapping phenomenon. In the absence of a parallel histologic examination of the injection specimens these features could not be revealed.

*Juxtamedullary aglomerular arterioles* — A much disputed question in intrarenal vascular anatomy has been whether all the blood reaching the medulla passes through glomeruli or whether there are aglomerular (arteriolae rectae verae) as well as glomerular routes (arteriolae rectae spuriae). It has often been asserted that aglomerular medullary pathways do not exist (11 43 54 56 65) or that they occur in the normal kidney to only a small extent (3 9 24 31 37 38 44 52, 57 58 63 70). More numerous aglomerular medullary vessels have been reported in supposedly but not histologically confirmed, pathologic kidneys (24 28 29 49 57 70 71). In the present investigation it was found that aglomerular vessels to the medulla occur from the seventh fetal month; that they increase in number with age and are still more numerous in hypertension and pyelonephritis. They were found to occur in degeneration of juxtamedullary glomeruli as was suspected earlier but could not be proven in the absence of histologic examination of injection specimens (38 44 52, 58 70). If the arteriolae rectae verae actually exist and develop as a result of glomerular degeneration, they should, it is held, not be present in the young kidney (47). This supposition has proved incorrect, since even in fetal life glomeruli in the pelvic and juxtamedullary connective tissue degenerate with the formation of arteriolae rectae verae (11).

*Pelvic aglomerular arterioles* — The studies have shown that the medulla is supplied to some extent by arterioles that derive from the area of the renal pelvis. Such vessels have also been observed earlier (1 18 31 43). De Sanctis (18) and Baker (1) considered that they supplied only the papillae and that damage to these arterioles or to the pelvic vascular system might be one cause of renal papillary necrosis. In the normal adult kidney similar vessels were observed that curved over the calyceal recess and passed down towards the papilla as bundles of arteriolae rectae (1). Their origin could not, however, be traced to the vascular plexus of the renal pelvis; instead they appeared to come from the pelvic ends of the renal columns, where they were evidently given off by interlobar or arcuate arteries. From the studies of the fetal kidney (11) it was found that these arterioles originated as arteriolae rectae verae on degeneration of glomeruli in the pelvic connective tissue and that the preglomerular segments of the arterioles gave off vessels to the connective tissue of the pelvic wall. After the glomeruli had degenerated the arterioles might therefore be expected to appear as branches from the pelvic plexus but in fact the opposite was the case. It was also found that the whole of the medullary pyramid was supplied by arteriolae rectae from the juxtamedullary zone and that these too reached the papilla (I II); thus De Sanctis and Baker did not examine. Nor in the case of renal papillary necrosis were there vascular changes restricted to the vessels deriving from

the pelvic region instead there was a depletion of vessels along the corticomedullary junction and in the medulla (V). In one case of hypertension in a newborn associated with unilateral renal artery stenosis the area supplied by the arteriole rectae coming from the pelvic wall was indirectly demonstrated (48). For the intrarenal ischaemia and hypotension due to the stenosis had led to necrosis of all the pyramids except the areas supplied by these arterioles. As they derived from wide interlobar arteries, they were probably less affected by the hypotension, and their area of supply therefore remained intact. This was seen as a thin sub-epithelial zone extending from the calyceal recess down over the tip of the papilla.

*Comparison between the different types of aglomerular arterioles* — The fact that the cortical arteriole-glomerular unit on the one hand and the juxtamedullary and pelvic units on the other degenerated in different manners is remarkable. The crucial point was found to be that in the case of a cortical glomerulus the whole of the unit degenerates, whereas in the case of the pelvic or juxtamedullary glomerulus (except in pyelonephritis when the postglomerular vessels are lost) there is direct contact between the afferent and efferent arterioles, and consequently the terminal extent of the unit, with the arteriole rectae leading to the medulla, remains intact. This suggests that there is normally an anatomic dissimilarity between the cortical glomeruli on the one hand and the juxtamedullary and pelvic on the other. In spite of the numerous stud-

ies of the structure of the glomerular tuft, only one has been found in which a comparison has been made between the cortical and juxtamedullary ones (75). In that study it was found that the juxtamedullary glomerular tuft, unlike the cortical one, has an anastomosis between the afferent and efferent vessels at the vascular pole. Owing to the dense vascularity of the glomerular tuft evident in the micro-angiograms, it was impossible to study its vascular arrangement more closely. However the observed changes in the arteriole-glomerular units were in agreement with the findings reported by Zlabek (75) and suggested that in degeneration of the juxtamedullary and pelvic arteriole-glomerular units the anastomosis remains intact and an aglomerular arteriole forms *via* the glomerular scar an anastomotic feature not encountered in the cortical unit.

### The intrarenal arterial pattern in hypertension

The increase in the number of arteriole rectae *verae* with age and their greater number in essential hypertension and pyelonephritis at expense of the arteriole rectae *spuria* implies a better anatomic basis for the medullary circulation and hence the possibility of a corresponding reduction in that of the cortex. If moreover vascular changes occur in the cortex, as was especially the case in essential hypertension and often in chronic pyelonephritis, there would be a still greater tendency for the blood to pass *via* the medulla, with cortical

ischaemia as a consequence. It has been established by experimental work (25, 26) and from medical experience that renal ischaemia may give rise to arterial hypertension. There is experimental evidence that it is the reduced blood supply to the cortex that is responsible for the development of hypertension in renal ischaemia (68). If this is also the case in man, the occurrence of hypertension in the present material would be explained by the cortical ischaemia that might well result from the changes in the arterial patterns of the diseased kidneys. It remains to be established, however, whether the renal vascular changes in hypertension are primary or a result of the rise in blood pressure. Whereas the investigation provides no explanation of the pathogenesis of essential hypertension, it has shown clearly that when hypertension has developed, changes are to be found in the intrarenal arterial pattern which provide an anatomic basis for cortical ischaemia to which the progress of the hypertension may be ascribed.

In the pyelonephritic kidneys there was a less well defined alteration of the juxtamedullary vascular anatomy than in the kidneys from patients with essential hypertension. While there is no doubt that arterioles rectae verae were formed as a result of glomerular degeneration, there were degenerated juxta-medullary glomeruli that had no post-glomerular vessels. A structural explanation of this was found in the severe periglomerular fibrosis, especially around the vascular pole, which might constrict the arterioles in the pole, partic-

ularly the thin walled efferent one — a possibility also suggested by Pfeiffer (62). A further explanation of the depletion of postglomerular vessels is to be found in the interstitial inflammation. Many of the pyelonephritic kidneys also exhibited signs of impaired postglomerular circulation in the juxtamedullary zone, for there was a collateral adaptation of still quite patent vessels and even necrosis of the dependent areas, that is the papillae (V). It thus appears to be clear that the vascular changes in the juxtamedullary zone in chronic pyelonephritis led either to anatomically improved (formation of arterioles rectae verae) or impaired (loss of postglomerular vessels) conditions for the medullary circulation, and that, if vascular changes occurred in the rest of the cortex these would contribute to the deterioration of the cortical circulation to a varying degree. Whether a cortical segment of a kidney would become ischaemic, with hypertension as a consequence, would depend chiefly on the type of change in the juxtamedullary vascular anatomy that would determine the balance between the cortical and medullary circulation in the area. The presence of vascular changes in the cortex would then be only a contributory cause of hypertension and not the main, or sole, one as has earlier been suggested (72). This argument would also explain the previously puzzling fact that hypertension is often found in chronic pyelonephritis even when the changes in the walls of the cortical vessels are relatively mild (13) and that the vessel walls may pre-

sent severe changes in the absence of hypertension (13-41).

Although cortical ischaemia should thus be offset by an improvement in the medullary circulation this does not rule out the possibility that renal papillary necrosis may also be accompanied by hypertension, since the pyelonephritic tissue changes may vary in character from one region to another in the same kidney. However hypertension would be less likely to occur in chronic pyelonephritis where there is papillary necrosis than where this is not present, this has been found to be the case (8-33).

The increase in the number of degenerated glomeruli appearing with age, and especially in hypertension and chronic pyelonephritis, might provide an anatomic explanation for the gradual development of renal failure in these pathologic conditions. It has been taken for granted that the whole arteriole-glomerular unit degenerates, but in the present investigation this was found to be the case only for the cortical units.

It is evident that the increase in number of aglomerular juxtamedullary arterioles resulting from the progressive degeneration of the glomeruli will inevitably affect the intrarenal haemodynamics and the renal function; this seems not to have been realised hitherto, since the existence of such arterioles has not been so convincingly demonstrated that it has been generally accepted. The functional importance of these arterioles cannot, however be demonstrated by purely morphologic studies on injection specimens. It is suggested above that they might well lead to a latent or manifest cortical ischaemia, and hence also to hypertension. A reliable guide to the significance of the aglomerular juxtamedullary arterioles to the intrarenal haemodynamics and the function of the kidney would be provided by experimental induction of hypertension or pyelonephritis in animals, with a graded comparative study of renal function as a whole, renal circulation and vascular morphology.

## General Summary

An investigation has been performed of the arterial tree of the normal and diseased human kidney using a combination of stereo-micro-angiographic and histologic techniques. This provided the following advantages over earlier investigations, none of which have included histologic examination of the tissues: (i) the state of the normal material was verified histologically; (ii) the type of pathologic tissue changes was diagnosed; (iii) the vessels studied in the micro-angiograms were followed in the histologic sections through the renal tissue and their positional relationship to the other structures thus determined; (iv) it was possible to decide if filling defects observed in the injection specimens were artefacts resulting from incomplete filling of normal vessels or whether they were due to structural changes; (v) it could be decided whether the contrast medium seen in the micro-angiograms represented vessels or leakage into the tissue through ruptured vessels.

The material consisted of 135 normal kidneys ranging in age from the beginning of the fourth fetal month to 79 years, 15 kidneys from cases of benign and 3 from cases of malignant hypertension, and 30 kidneys from cases of chronic pyelonephritis with and without renal papillary necrosis and with and without hypertension.

In normal ageing kidneys and in hypertensive and pyelonephritic kidneys the periglomerular cortical vessels were

spiralled. Possible causes of this were (i) interstitial fibrosis with shortening of the distance between the terminal points and (ii) elongation of the vessels between the stationary points, representing a collateral reaction due to obstruction or depletion of other vessels. In the renal pelvis spiralling vessels occurred normally.

In the pyelonephritic kidneys with renal papillary necrosis vascular changes were observed in the medulla: dilatation, spiralling and thickening of the walls of the arterioles rectae — evidence of collateral adaptation. This suggested that the inflammatory exudate and/or the periglomerular fibrosis in the juxta-medullary zone constricted efferent vessels leading to the medulla, so that collateral adaptation tended to develop. If this adaptation was inadequate papillary necrosis occurred.

In the youngest of the kidneys examined there were well developed arteriole-glomerular units in the connective tissue of the renal pelvis and in the juxta-medullary zone. At the end of the fourth fetal month there was a typical medullary vascular pattern with arterioles rectae spuriae given off by efferent arterioles of pelvic and juxtamedullary glomeruli. Postglomerular vessels in the cortex did not appear until the eighth fetal month. These conditions were considered as evidence that the intra-renal circulation up to about the eighth fetal month took place *via* the medulla.

During the seventh fetal month arterioles rectae verae were seen these developed as a result of contact being established between the afferent and efferent arterioles through degenerated glomeruli in the pelvic connective tissue and the juxtamedullary zone. From the afferent pelvic arterioles branches were given off to the pelvic connective tissue. In the cortex the glomerular degeneration led to atrophy also of the afferent and efferent vessels.

The fact that the cortical on the one hand and the pelvic and juxtamedullary arteriole-glomerular units on the other undergo different changes in glomerular degeneration suggests that there is an anatomic difference between the glomeruli of these areas. The latter type of glomerulus probably has a connection between the afferent and efferent arterioles which the cortical one lacks, and which, in the degeneration of the glomerular tuft itself does not degenerate but gives rise to a direct continuity between the afferent and efferent vessels.

The increasing frequency of degenerated glomeruli with age and the pathologically high number in hypertension and pyelonephritis led to an increase in the number of atrophied arteriole-glomerular units in the cortex and arterioles rectae verae to the medulla. This implies anatomically less favourable conditions for the cortical circulation and better conditions for the medullary one. The development of hypertension would then be ascribable to the cortical ischaemia accompanying the vascular changes. In cases of chronic pyelonephritis, however postglomerular vessels from the juxtamedullary zone are also lost, so that the otherwise favourable conditions for the medullary circulation are impaired. This would explain the less regular occurrence of hypertension in these cases. A contributory cause of cortical ischaemia, and hence hypertension might be found in the often marked thickening of the walls of the cortical vessels.

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# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 409

## MORTALITY OF PEPTIC ULCER PATIENTS

*Accompanies Vol. 174*

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*To Hans Jacob Ustvedt  
whose initiative brought about the establishment of the Institute  
on his sixtieth birthday*



*The material for this study was collected from the following departments of the Ullevål Hospital:*

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## *1 Introduction*

The purpose of the present study can be stated as follows

- a) To provide total mortality rates for operated and non-operated peptic ulcer patients and to compare the rates with those of the general population.
- b) To study the association – positive or negative – of peptic ulcer with other diseases.
- c) To search for late complications after operations for peptic ulcer

Cause-specific mortality rates have been used as the index for b) and c) above. This index has the serious limitation that it does not provide information on non fatal associated diseases or non-fatal complications of peptic ulcer operations. Thus, it will not be possible to elucidate the relationship between peptic ulcer and say psoriasis or to describe the incidence of anaemia or dumping syndrome following operation.

On the other hand, mortality as an index has the advantage that reasonably precise comparisons can be made with the general population. Also, of course, practical difficulties are much smaller in describing the mortality in a patient group than in describing incidence.

## 2 *Material and Methods*

### MATERIAL

The material is based on the diagnostic files from the years 1917-39 in the following departments of the Ullevål Hospital

Departments II and III (Surgical) and Departments VII, VIII and IX (Medical)

All patients were registered who had a diagnosis of *Ulcus ventriculi*, *Ulcus pylori*, or *Ulcus duodeni*, with or without a question mark or such qualifications as *penetrans* or *perforans*

The patient records were studied and information extracted in code. The following number of patients, originally found in the diagnostic files, have been excluded from the rest of this report

Record not located	12
Patients transferred to other department and not discharged until 1940	4
Patient transferred to other department which did not sustain the diagnosis	66
Other cases where the discharge diagnoses did not include gastric or duodenal ulcer	21
Patient had a gastric or duodenal operation prior to first registered stay	78
Patient residing outside Oslo (1948 boundary) at time of admission	108
Patient died during first registered stay	153

This leaves the group which will be described in this report 3 662 persons, Oslo residents at time of admission, with no gastric or duodenal operation prior to first stay and discharged alive in 1917-39 with gastric or duodenal ulcer as one of the discharge diagnoses.

Table I shows the material according to sex, diagnosis, and calendar year of discharge.

The two sexes differ markedly both in number of patients and in diagnostic distribution. The Table also illustrates clearly the diagnostic shift that occurred from gastric to duodenal ulcer between the two world wars.

Appendix I gives information on the symptomatology and the intensity of diagnostic work up in the material. The proportion of patients with haematemesis or melaena decreased during the period 1917-39 whereas the acid production increased, as measured by the amount of free acid<sup>1</sup> at the Ewald test meal. X ray was rarely used in 1917-19 both prior to admission and during the registered stay. In 1935-39 about 80 % were examined during

Table 1

Number of patients by sex and calendar year of first discharge. Percentage diagnostic distribution for each subgroup

Year of first discharge	Number of patients	Percentage distribution Type of diagnosis			Total
		Ulcer ventriculi (not marked as doubtful)	Ulcer duodeni (not marked as doubtful)	Other (incl. Ulcer pylori and diagnoses marked as doubtful)	
MALES					
1917-19	172	76.2	17.4	6.4	100.0
1920-24	283	39.0	33.9	7.1	100.0
1925-29	383	54.8	33.4	11.8	100.0
1930-34	663	31.7	35.7	12.6	100.0
1935-39	912	26.8	63.4	9.8	100.0
All years	2,419	39.9	49.7	10.4	100.0
FEMALES					
1917-19	207	93.2	2.9	3.9	100.0
1920-24	203	79.5	11.7	8.8	100.0
1925-29	205	69.8	18.5	11.7	100.0
1930-34	268	43.3	40.7	16.0	100.0
1935-39	338	37.5	54.7	7.8	100.0
All years	1,243	60.5	30.0	9.7	100.0

the stay. The large proportion of negative X ray examinations in the hospital can largely be ascribed to the fact that if an ulcer had been roentgenologically demonstrated prior to admission a new X ray was taken only after a period of treatment.

#### METHODS OF FOLLOW-UP

The patients were traced through the population registers, through the hospital admission registers of the Ullevål and Aker Hospitals, or by correspondence with relatives, friends, and neighbours. An attempt was made to trace the 3 662 patients either until death or to the anniversary of discharge in 1957. The result was as follows:

	Males		Females	
	No.	Per cent	No.	Per cent
Died after discharge, but prior to anniversary of discharge in 1957	910	37.6	462	37.2
Lost from observation	38	1.6	71	5.7
Alive at anniversary in 1957	1 471	60.8	710	37.1
	2,419	100.0	1,243	100.0

Autopsy results were collected for 402 male deaths (44 %) and for 159 female deaths (34 %).

Of the deaths, 8 per cent occurred after the patient had moved from Oslo. Of the living patients 16 per cent resided outside Oslo in 1957

The death certificates were searched for in the Central Bureau of Statistics and the original cause-of-death code was copied. In 52 cases where the cause of death was known, but where the original code could not be found (including some who died outside Norway) the cause was coded for us in the Central Bureau of Statistics to the classification which was in use in the year of death.

In 8 cases, 6 males and 2 females, no information is available as to the cause of death.

Some of the patients in the material were operated during first registered stay. For those who were initially discharged unoperated it was necessary to ascertain whether they had an ulcer operation at any time later. The following procedure was used.

The records for re-admission to Ullevål Hospital and records for any admission to Aker Hospital were studied. To those patients who were alive and whose operation status was not clear a questionnaire was then mailed, followed by a reminder. The letter asked whether the patient had ever undergone an operation which might have affected the stomach or duodenum, and if so, when and where. An answer was obtained from 97 % of about 1 000 patients addressed in this manner. 17 % of those who answered the first letter had been operated, against 21 % of those who answered the reminder.

For those patients who were initially discharged unoperated and who had later died in a hospital information was obtained on operation status at death, either by study of the record or by correspondence with the hospital. For those who died outside hospital, and for those whose record did not contain sufficient information, personal letters were sent to relatives or friends, identified through the population registers or hospital documents.

All reported operations were investigated as far as possible, either through study of the hospital record or through correspondence with the hospital or surgeon. The information received from patients, and also from relatives, turned out to be surprisingly accurate.

In this study a patient has been counted as operated only if he was subjected to one of the following procedures: Resection of the stomach with gastroduodenal or gastrojejunal anastomosis, gastrojejunostomy, resection circularis, or vagotomy.

Patients who only had an excision or suturation of the ulcer and patients who were subjected to pyloroplasty (Judd), duodenoplasty, gastrostomy, duodenostomy or gastro-duodenostomy (Finney) were considered to be still unoperated and were followed up for further operations.

No systematic attempt was made to register re-operations. However some patients who have been classified as having had a gastrojejunostomy are known to have had a resection later.

The follow up results with respect to operation status were as follows:

	Males		Females	
	Number	Per cent	Number	Per cent
Operated during first stay	493	70.4	159	11.2
Operated later	781	32.5	188	15.1
Operation status unknown at death or in 1957	65	2.7	95	7.6
Still unoperated at death or in 1957:	1,080	44.6	821	66.1
	2,419	100.0	1,243	100.0

Those whose operation status was unknown at the end of the observation period have been counted as *not* operated in the analysis. This introduces only a small error, as we have established that they were not operated at Ullevål or Aker Hospitals, where most of the operations in the material took place.

The type of operation was as follows:

	Number of patients	
	Males	Females
Operated for ulcer		
Resection with gastroduodenal or gastrojejunal anastomosis	751	200
Resectio circularis	2	15
Gastrojejunostomy	471	99
Type of operation unknown, but most probably one of the preceding types	17	8
Vagotomy	5	0
	1,244	320
Operated for cancer of the stomach	30	7
	1,274	327

Most of the resections have been performed according to the Billroth II method.

The operations after first discharge took place in the following hospitals:

	Number of patients	Per cent
Ullevål	619	63.9
Aker	66	6.8
Other hospitals in Oslo	226	13.3
Other Norwegian hospitals	47	4.9
Hospitals in other countries	31	1.1
	969	100.0

#### METHODS OF COMPILATION

The observation years in this material cover a period during which mortality rates for various age-sex-cause groups have changed greatly. Also the method of compilation of official mortality statistics has undergone changes. It was therefore thought desirable to distribute the observation years by sex, 10-year



groups of age attained, and the following eight calendar year groups 1917-21 1922-6 1927-30 1931-5 1936-40 1941-5 1946-50 and 1951-7. The choice of groups was dictated by the fact that new cause-of-death classifications were introduced in 1927 1941 and 1951.

However it was also necessary to take account of time from the start of the observation period. Accordingly the observation years in each of the above mentioned subgroups were divided as follows:

Unoperated state

Years after first discharge	0-4
	5-14
	15 +

Operated state

Years after operation	0-4
	5-14
	15 +

A method of distributing the observation years in this manner was devised by RIs and is described in an Addendum to this report.

Finally the observation years in each of the resulting subgroups had to be divided according to location of ulcer and type of operation.

It was not feasible to define gastric and duodenal ulcers among unoperated patients by means of objective findings stated in the records. Instead the division of the material was made on a basis of the discharge diagnosis. The observation years for operated state were subdivided according to the findings at the operation. Only patients who had either a resection (excluding resection circularis) or a gastrojejunostomy have been included in the analysis according to ulcer site and operation type.

Pyloric ulcers were not numerous enough to warrant a separate analysis. They have been grouped together with duodenal ulcers, in accordance, for instance, with Doll *et al* (1).

The diagnostic subgroups in the material are then defined as follows:

*NOT OPERATED*

*Gastric ulcer* Discharge diagnosis specified as *ulcus ventriculi*, with or without penetration or perforation, but without indicated doubt or possible malignancy and without indicated duodenal or pyloric ulcer.

*Duodenal ulcer* Discharge diagnosis specified as *ulcus duodeni* or *ulcus pylori*, with or without penetration or perforation, but without indicated doubt or possible malignancy and without indicated gastric ulcer.

*OPERATED*

*Gastric ulcer* Non-malignant gastric ulcer (or scar) specified as found at resection or gastrojejunostomy without specified duodenal ulcer.

*Duodenal ulcer* Non-malignant pyloric or duodenal ulcer (or scar) specified as found at resection or gastrojejunostomy without specified gastric ulcer.

It is clear from these definitions that whereas the operated material gets a high diagnostic precision, the diagnosis will remain doubtful in many cases in the unoperated material.

Patients who died postoperatively i.e. before they had been discharged from hospital after their first operation as defined in this study have had their entire observation period counted in the unoperated group. Similarly these deaths have all been counted as occurring among unoperated patients.

Patients who were operated because of cancer of the stomach present a special problem. In the total material there were 83.0 observation years for males and 35.0 for females after such an operation. Deaths from stomach cancer in this group should be regarded as occurring among unoperated ulcer patients, because the cancer caused the operation. On the other hand one might argue that deaths from other causes, such as coronary heart disease, belong in the operated group, because the relationship between gastric resections and coronary heart disease might be independent of the reason for resection. However only one of the 29 deaths among patients operated for cancer of the stomach was due to another cause (pulmonary tuberculosis) so that the mortality risk from other causes is of little consequence. In the present study therefore, all observation years and all deaths among patients operated for cancer of the stomach have been referred to the unoperated group.

Table 2 shows the total number of observation years in the material, distributed by calendar year, age, sex, and operation status.

It will be seen that the observation years under 20 years of age are few. Two deaths occurred in this group, one male and one female, both unoperated. From the rest of the report age under 20 will be excluded.

Table 3 compares the number of observation years at age 20 and over in the total material with the number included in the analysis by site of ulcer and type of operation, as defined above.

The observation years in each sub-group have been multiplied by population death rates for corresponding sex, age, and calendar year group to provide expected numbers of death. The Institute has computed such death rates for the following groups:

- |        |   |
|--------|---|
| Norway | Mortality from all causes and from 39 cause groups for all calendar year periods.   |
| Oslo   | Mortality from all causes for all calendar year periods. Mortality from 39 cause groups for the period 1931-7. Mortality from 13 cause groups for the periods 1941-5 and 1946-50. |

The number of deaths from the various causes in Norway have been taken from the Norwegian Medical Statistical Reports, supplemented by manuscript data on deaths outside Norway during the second world war. For the years prior to 1928, when the deaths tabulated in the Medical Statistical Reports fell short of the true total, the deaths from all causes have been taken from the Norwegian Vital Statistics Reports. The population data have been taken from the Norwegian Life Tables 1911/12-1920/21 1921/22-1930/31 1931/32-

Table 2

Number of observation years in total material by operation status, sex, age attained, and calendar year

Calendar years	Age in years								All ages
	Under 20	20-29	30-39	40-49	50-59	60-69	70-79	80 and over	
NOT OPERATED									
Males									
1917-21	13.0	113.0	108.5	99.5	58.0	44.0	6.0	-	444.0
1922-26	22.0	299.0	356.5	243.0	170.0	98.0	23.0	1.5	1,213.0
1927-30	8.0	316.0	330.5	297.0	248.5	118.5	4.5	4.5	1,565.5
1931-35	27.0	559.0	1,178.0	774.5	491.0	262.0	93.5	13.0	3,390.0
1936-40	77.5	799.5	1,799.5	1,619.0	873.0	508.5	127.0	35.5	5,839.5
1941-45	26.5	391.0	1,418.0	1,800.0	1,138.5	570.5	223.5	39.5	5,617.5
1946-50	-	73.0	734.5	1,574.0	1,250.0	623.5	309.0	43.5	4,991.5
1951-57	-	7.5	287.5	1,212.0	1,673.0	1,023.0	470.0	94.0	4,719.0
1917-57	174.0	2,562.0	6,413.0	7,427.0	5,832.0	3,250.0	1,296.5	233.5	27,189.0
Females									
1917-21	34.0	255.0	154.5	96.0	60.0	28.0	18.5	6.5	632.5
1922-26	26.0	441.5	361.0	234.5	175.0	100.0	56.0	15.0	1,587.0
1927-30	9.0	336.5	430.5	276.0	170.0	168.0	48.0	10.0	1,568.0
1931-35	23.5	337.5	782.0	504.5	444.0	332.0	157.5	20.5	2,628.5
1936-40	25.0	360.0	897.5	907.5	620.5	548.5	268.5	43.0	3,690.5
1941-45	2.0	158.0	666.5	1,079.5	723.0	598.5	348.0	87.5	3,663.0
1946-50	-	28.5	3.8.5	883.0	831.0	572.5	373.0	137.5	3,189.0
1951-57	-	1.5	141.0	668.5	1,233.0	805.0	563.0	181.0	3,995.0
1917-57	119.5	1,938.5	3,018.5	4,634.5	4,356.5	3,135.5	1,834.5	499.0	20,373.5
OPERATED									
Males									
1917-21	1.5	51.0	33.5	57.5	21.0	19.0	4.0	-	187.5
1922-26	10.0	159.0	197.5	134.0	102.0	53.0	14.5	-	676.0
1927-30	12.5	170.0	418.5	195.5	149.0	87.0	29.0	2.5	1,064.0
1931-35	12.5	256.5	833.5	526.5	255.0	167.0	46.0	6.5	2,103.5
1936-40	7.0	301.0	1,046.5	1,058.0	452.5	269.5	76.5	10.5	3,221.5
1941-45	3.5	163.0	987.0	1,602.0	814.0	369.0	113.0	12.0	4,063.5
1946-50	.5	44.5	663.0	1,689.5	1,529.5	549.5	190.5	27.0	4,494.0
1951-57	-	10.0	271.5	1,540.0	1,293.5	1,049.0	363.0	82.0	3,614.0
1917-57	47.5	1,135.0	4,451.0	6,803.0	5,416.5	2,699.0	641.5	140.5	21,424.0
Females									
1917-21	-	2.5	22.0	17.5	21.0	13.5	-	-	76.5
1922-26	-	19.0	49.5	68.5	73.0	51.5	.5	.5	262.5
1927-30	-	11.5	69.5	89.5	86.0	71.0	13.0	-	340.5
1931-35	5.5	40.0	111.5	131.5	156.0	99.0	49.0	-	592.5
1936-40	4.5	71.0	157.0	193.0	230.5	150.0	76.5	9.5	894.0
1941-45	-	41.5	177.0	245.0	247.0	232.0	88.0	28.5	1,059.0
1946-50	-	14.5	125.5	269.0	269.0	250.0	129.0	49.5	1,106.5
1951-57	-	.5	68.0	317.0	372.5	333.5	238.5	66.0	1,396.0
1917-57	10.0	200.5	780.0	1,333.0	1,453.0	1,200.5	594.5	151.0	5,727.5

1940-41 and 1946-50 From 1951 onwards population estimates have been taken from the Norwegian Vital Statistics Reports.

The following points may be noted about the processing of death certificates in Norway

Table 3

Observation years, age 20 and over in total material compared to observation years in analyses according to ulcer site and type of operation

	MALES		FEMALES	
	Number of observation years, age 20 +		Number of observation years, age 20 +	
	Total material	Material analyzed by ulcer site and operation	Total material	Material analyzed by ulcer site and operation
NOT OPERATED				
Gastric ulcer		11,382.5		13,192.0
Duodenal ulcer		12,694.0		5,200.0
Total	27,014.0	24,076.5	20,254.0	18,392.0
OPERATED				
Gastric ulcer				
Resection		2,074.5		1,067.5
Gastrojejunostomy		1,333.0		422.0
Duodenal ulcer				
Resection		7,737.5		1,493.5
Gastrojejunostomy		6,599.5		1,225.0
Total	21,576.5	17,984.5	5,717.5	4,208.0

Prior to 1925 tabulation of cause-of-death statistics was decentralized. The District Health Officers submitted tables, by age, sex, and cause, of deaths occurring in their district. The Central Bureau of Statistics has processed the individual certificates from 1925 onwards.

During the years 1917-26 the classification of 1911 was in use. However in 1919 this classification was supplemented by an additional list for malignant tumours of various sites. The rates used in this report for the periods 1917-21 and 1922-6 for cancers of the lung, pharynx, larynx, and oesophagus have been based on the returns on these lists. (The returns for 1919-21 have been taken to represent the period 1917-21.) Deaths among ulcer patients in these periods have been referred to one of the four cancer types if so indicated by the cause written on the certificate.

In 1927 a more detailed Scandinavian cause-of-death list was introduced. This was succeeded in 1941 by the International 1938-list. From 1951 onwards the Sixth Revision of the International Statistical Classification has been used together with the International Certificate for Cause of Death. The discontinuity of the time trend for cause-of-death statistics caused by the 1951 revision was greater than that resulting from any of the previous two revisions.

Further details about the basis for Norwegian mortality statistics have been given by Backer (2).

The choice of cause-of-death groups was the result of two main considerations. First, causes were selected which by previous studies had been indicated as possibly related to peptic ulcer. Examples are cancer of the stomach and

tuberculosis of the lungs. Secondly an attempt was made to define cause groups which had more or less the same content throughout the period 1917-57 despite changes in nomenclature and classification, even if no particular relationship was expected. Examples of such groups are syphilis, appendicitis, and deaths from non natural causes.

Coronary heart disease is the most typical example of a disease which was thought to be of sufficient interest to warrant a separate group even if it is impossible to select groups prior to 1951 whose definition strictly corresponds to the definition of coronary heart disease given by the Sixth Revision of the International Statistical Classification. Many deaths which today would be labelled as due to coronary heart disease or myocardial degeneration were previously referred to other categories of heart disease.

The death rates computed by the Institute should not be used for study of mortality time trends, except with the utmost caution. The point here, however is that within each period the Institute has distributed the deaths among the ulcer patients according to the original cause code of the Central Bureau of Statistics. Comparisons have then been made with general mortality from identical code numbers. This comparison would presumably be unbiased even if the content of the group varies from one classification period to another.

Appendix II shows the cause groups used in this study defined by means of the included code numbers in the four classification periods.

It should be noted that the following five groups were included only after a preliminary study of the data had indicated that the number of deaths might be above expectation for these groups: Cancer of pharynx, cancer of larynx, cancer of lung, cancer of oesophagus and suicide.

In many deaths the official cause code does not correctly summarize what is actually known about the cause of death. Therefore, all deaths in the material were reviewed and a revised code number (using the 39 groups as defined in Appendix II for 1951-7) assigned on the basis of the total evidence available. Appendix III shows a cross-tabulation of the official and revised codes for the 1 370 deaths in the material which occurred at age 20 and above. It can be seen from this Table that for 79.6 % of the deaths the official and revised codes were identical. This percentage did not vary much among subgroups of the material.

#### NOT OPERATED

Males 79.5

Females 77.4

#### OPERATED

Males 82.3

Females 78.5

Most of the deaths where the official and revised codes differed belonged to the 40 % of the material for which autopsy results were available. However there were also cases where a hospital stay shortly prior to death provided information which contradicted the death certificate.

In the analysis the distribution by the official code will be supplemented by the distribution according to the revised code.

All patients in the material were living in Oslo at the start of the observation

period, and most of them were still Oslo residents at the end of observation. It is therefore desirable, as far as possible, to compare the mortality in the material with the Oslo mortality in addition to the mortality in Norway. This is particularly important for cause groups where the differences between the Oslo and Norwegian rates are large, such as for lung cancer and coronary heart disease.

For the period 1951-7 the Central Bureau of Statistics has prepared the Oslo statistics, and the comparison presents no problem. In previous years, however the Oslo Health Department coded the death certificates before passing them on to the Central Bureau of Statistics and prepared its own tabulations. The Scandinavian list, which was discontinued by the Central Bureau of Statistics in 1941, was in use in Oslo up to and including 1950. The Institute has selected for comparison only a few causes in the Oslo mortality experience for the periods 1941-5 and 1946-50. The groups chosen are thought to be relatively little influenced by differences in coding practice and by the fact that the classification in use in Oslo in those periods was different from the one used for Norway. The Institute has computed the rates on the basis of the deaths published in the reports of the Oslo Health Department. Population estimates have been prepared by the Institute on the basis of data from the Municipal Office of Statistics. It should be noted that the city of Oslo was expanded on 1 January 1948 to include Åker. Prior to that date, the data from which the rates have been computed refer only to the old city area.

We have not considered it worth while to make comparisons with Oslo data (except mortality from all causes) prior to 1941.

The rates from which the Institute has computed expected numbers are shown in

Appendix IV Rates for Norway, all calendar year periods, for the groups defined in Appendix II and for total mortality.

Appendix V Rates for Oslo, all calendar year periods, total mortality.

Appendix VI Rates for Oslo, 1951-7, for the groups defined in Appendix II.

Appendix VII Rates for Oslo, 1941-5 and 1946-50, for 13 cause groups.

Rates for a few other causes, to be mentioned in the text, have been computed for Oslo and Norway for the years 1951-7. These rates are not reproduced.

The expected number of deaths was computed to the nearest thousandth. In the Tables of this report they have been rounded to the nearest tenth. Sums and ratios have been computed from the detailed expectations, so that the rounded figures shown in the tables are not necessarily fully consistent.

Many of the comparisons made in this report were not planned in advance. Exact confidence limits and significance tests are therefore difficult to obtain. However, in order to facilitate a rough assessment of how often a difference of a certain size will occur by pure chance, confidence limits (99 %, 95 %, and 90 %) for the expectation of a Poisson variable have been given in Appendix VIII. The table is adapted from Pearson & Hartley (3) except for the entries for observed numbers 60 and higher which have been computed by the Institute.

### 3 Results

#### TOTAL MORTALITY

Table 4 shows actual and expected number of deaths from all causes in the total material, by operation status, sex, and age.

The over all mortality ratios (ratio between actual and expected deaths) are very similar for operated and unoperated patients. Based on Norwegian death

Table 4

Actual deaths (D) from all causes and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by operation status, sex, age attained, and calendar year

		Age in years								Age 20 and over	
		20-29	30-39	40-49	50-59	60-69	70-79	80 and over	20 and over	D/ $E_N$	D/ $E_O$
NOT OPERATED											
Males											
1917-21	D	1	2	1	2	3	1	-	10		
	$E_N$	1.2	.9	.8	.8	1.1	.4	-	5.4	1.87	
	$E_O$	7	.9	1.1	1.1	1.7	.5	-	5.9		1.69
1922-26	D	0	5	9	9	3	3	0	29		
	$E_N$	2.0	2.0	1.8	2.1	2.6	1.5	.3	12.2	2.38	
	$E_O$	1.5	2.2	2.4	3.2	3.8	2.0	.3	15.3		1.90
1927-30	D	3	7	7	3	11	5	2	38		
	$E_N$	1.8	2.9	2.1	3.0	3.1	2.6	.8	16.3	2.34	
	$E_O$	1.5	3.3	3.0	4.1	4.3	3.2	.8	20.4		1.86
1931-35	D	1	7	15	20	17	11	2	75		
	$E_N$	2.4	3.4	4.6	5.4	6.5	5.8	2.3	32.5	2.25	
	$E_O$	2.0	3.9	6.4	7.9	9.4	7.4	2.2	41.0		1.78
1936-40	D	4	11	19	17	26	12	8	90		
	$E_N$	3.2	7.8	9.5	9.5	12.4	7.9	6.4	56.6	1.59	
	$E_O$	2.0	7.7	15.9	14.2	18.4	10.9	7.2	74.3		1.11
1941-45	D	8	12	17	21	22	17	9	106		
	$E_N$	2.2	7.3	12.2	12.4	12.8	12.6	6.7	66.3	1.60	
	$E_O$	1.2	5.8	14.6	15.6	17.1	14.5	6.4	74.9		1.41
1946-50	D	2	1	7	24	10	20	10	74		
	$E_N$	.2	1.8	5.7	10.6	12.7	16.7	7.4	55.0	1.54	
	$E_O$	1	1.5	7.1	14.1	16.6	20.0	7.8	67.2		1.10
1951-57	D	0	1	6	22	44	35	15	121		
	$E_N$	.0	.5	4.1	15.9	21.4	25.4	14.2	79.5	1.52	
	$E_O$	.0	.5	4.7	18.3	28.3	30.9	15.0	97.7		1.24
All calendar years	D	19	46	81	113	156	104	42	541		
	$E_N$	12.8	28.9	40.8	57.6	72.6	72.9	38.0	323.7		
	$E_O$	9.0	27.5	53.1	78.4	99.7	89.4	39.7	396.8		
All calendar years	D/ $E_N$	1.48	1.59	1.98	1.96	1.87	1.43	1.10	1.67		
	D/ $E_O$	2.11	1.67	1.52	1.44	1.36	1.16	1.06	1.36		

Table 4 (cont.)

		Age in years								Age 20 and over	
		20-29	30-39	40-49	50-59	60-69	70-79	80 and over	90 and over	D/E <sub>75</sub>	D/E <sub>90</sub>
NOT OPERATED											
Females											
1917-21	D	4	1	4	1	1	0	0	11	1.47	1.56
	E <sub>75</sub>	2.1	1.2	.8	.7	.6	1.1	1.1	7.5		
	E <sub>90</sub>	1.5	1.0	.7	.8	.8	1.2	1.1	7.0		
1922-26	D	3	2	8	2	3	4	2	24	1.73	1.74
	E <sub>75</sub>	2.4	1.9	1.5	1.8	2.2	2.0	2.1	13.8		
	E <sub>90</sub>	1.6	1.5	1.7	2.1	2.4	2.5	2.2	13.8		
1927-30	D	2	6	5	1	5	1	2	32	1.58	1.33
	E <sub>75</sub>	1.5	2.1	1.7	2.7	3.6	2.6	1.6	15.9		
	E <sub>90</sub>	1.2	1.8	1.7	3.0	4.3	3.0	1.6	16.5		
1931-35	D	1	2	6	7	7	9	3	35	1.17	1.12
	E <sub>75</sub>	1.2	3.1	2.7	4.2	6.8	8.6	3.3	29.8		
	E <sub>90</sub>	.9	2.5	2.6	4.4	7.6	10.0	3.3	31.3		
1936-40	D	0	3	4	11	18	24	8	68	1.44	1.32
	E <sub>75</sub>	.9	2.8	4.0	5.4	10.7	15.9	7.5	47.1		
	E <sub>90</sub>	.6	2.5	4.5	6.0	12.9	17.9	7.5	51.5		
1941-45	D	0	1	7	6	12	19	11	56	1.05	1.04
	E <sub>75</sub>	.4	1.9	4.3	5.5	10.6	16.7	13.7	53.1		
	E <sub>90</sub>	.3	1.6	4.4	3.2	11.4	18.1	13.0	54.0		
1946-50	D	0	0	1	8	8	29	21	67	1.17	1.17
	E <sub>75</sub>	.0	.6	2.7	5.2	9.3	17.8	21.6	57.5		
	E <sub>90</sub>	.0	.3	2.5	5.2	9.7	18.6	20.5	57.0		
1951-57	D	0	0	0	9	13	22	27	71	.97	.99
	E <sub>75</sub>	.0	.2	1.5	6.8	11.7	25.9	26.9	73.0		
	E <sub>90</sub>	.0	.1	1.4	6.9	12.0	26.0	25.5	71.7		
All calendar years	D	10	15	35	45	67	108	74	354		
	E <sub>75</sub>	8.6	13.7	19.1	32.4	55.5	90.6	77.7	297.5		
	E <sub>90</sub>	6.3	11.5	19.3	33.4	61.1	97.0	74.3	302.9		
All calendar years	D/E <sub>75</sub>	1.17	1.10	1.83	1.39	1.21	1.19	.95	1.19		
	D/E <sub>90</sub>	1.60	1.50	1.81	1.35	1.10	1.11	1.00	1.17		



Table 4 (cont.)

		Age in years								Age 20 and over	
		20-29	30-39	40-49	50-59	60-69	70-79	80 and over	20 and over	D/E <sub>N</sub>	D/E <sub>O</sub>
		OPERATED									
		Males									
1917-21	D	1	0	2	2	2	1	-	8	3.37	3.00
	E <sub>N</sub>	.5	.3	.5	.3	.5	.3	-	2.4		
	E <sub>O</sub>	.3	.3	.6	.4	.7	.4	-	2.7		
1922-26	D	1	4	0	2	2	1	-	10	1.45	1.14
	E <sub>N</sub>	1.0	1.1	1.0	1.3	1.5	.9	-	6.9		
	E <sub>O</sub>	.8	1.2	1.3	1.9	2.3	1.3	-	8.8		
1927-30	D	1		1	4	3	4	0	15	1.57	1.08
	E <sub>N</sub>	1.0	2.3	1.4	1.8	2.3	1.8	.4	10.9		
	E <sub>O</sub>	.8	2.6	2.0	2.5	3.3	2.2	.4	13.8		
1931-33	D	2	8	12	5	8	8	1	44	2.31	1.82
	E <sub>N</sub>	1.1	3.8	3.2	2.8	4.2	2.9	1.1	19.1		
	E <sub>O</sub>	.9	4.2	4.3	4.1	6.0	3.6	1.1	24.2		
1936-40	D	4	9	12	10	3	6	3	47	1.57	1.17
	E <sub>N</sub>	1.2	4.5	6.2	4.9	6.6	4.7	1.9	30.0		
	E <sub>O</sub>	.8	4.5	9.1	7.4	9.7	6.6	2.1	40.1		
1941-45	D	2	7	13	21	12	11	2	63	1.49	1.20
	E <sub>N</sub>	.9	5.2	10.8	8.9	8.3	6.3	2.0	42.4		
	E <sub>O</sub>	.5	3.9	13.0	11.1	11.0	7.3	1.9	48.7		
1946-50	D	1	6	11	29	11	13	7	78	1.69	1.37
	E <sub>N</sub>	1	1.6	7.0	11.4	11.2	10.3	4.4	46.0		
	E <sub>O</sub>	1	1.3	8.7	13.3	14.6	12.3	4.7	56.9		
1951-57	D	5	1	7	38	29	20	8	103	1.30	1.04
	E <sub>N</sub>	.0	.5	5.2	19.7	21.9	19.9	12.4	79.3		
	E <sub>O</sub>	.0	.4	6.0	25.9	29.0	24.2	13.1	98.6		
All calendar years	D	12	37	58	111	70	59	21	368		
	E <sub>N</sub>	3.8	19.4	35.2	51.0	56.4	47.1	22.3	237.2		
	E <sub>O</sub>	4.2	18.4	45.0	68.5	76.7	57.8	23.3	293.8		
All calendar years	D/E <sub>N</sub>	2.06	1.91	1.65	2.18	1.24	1.23	.94	1.53		
	D/E <sub>O</sub>	2.88	2.01	1.29	1.62	.91	1.02	.90	1.25		

Table 4 (cont.)

		Age in year							Age 20 and over		Age 20 and over	
		20-29	30-39	40-49	50-59	60-69	70-79	80 and over	20 and over	D/E <sub>M</sub>	D/E <sub>O</sub>	
OPERATED												
Females												
1917-21	D	0	2	0	1	0	-	-	3	3.30	3.26	
	E <sub>M</sub>	.0	.2	1	.2	.3	-	-	.9			
	E <sub>O</sub>	.0	1	1	.3	4	-	-	.9			
1922-26	D	0	1	0	2	0	0	1	4	1.43	1.33	
	E <sub>M</sub>	1	.3	4	.8	1.1	.0	1	2.8			
	E <sub>O</sub>	1	2	3	.9	1.3	.0	1	3.0			
1927-30	D	0	0	0	1	5	1	-	7	1.74	1.38	
	E <sub>M</sub>	1	.3	.3	.9	1.3	7	-	4.0			
	E <sub>O</sub>	.0	.3	.3	.9	1.8	.8	-	4.4			
1931-35	D	0	0	0	0	3	1	-	4	.54	.50	
	E <sub>M</sub>	1	4	7	1.3	2.0	2.7	-	7.4			
	E <sub>O</sub>	1	4	7	1.3	2.3	3.1	-	8.1			
1936-40	D	0	0	3	2	3	3	0	13	1.06	.96	
	E <sub>M</sub>	.2	.3	.9	2.0	2.9	4.2	1.6	12.3			
	E <sub>O</sub>	1	4	.9	2.2	3.3	4.7	1.6	13.6			
1941-45	D	1	3	2	4	3	3	4	22	1.33	1.33	
	E <sub>M</sub>	1	.3	1.0	1.9	4.1	4.2	4.4	16.3			
	E <sub>O</sub>	1	4	1.0	1.8	4.4	4.6	4.2	16.3			
1946-50	D	0	1	1	3	4	10	4	23	1.11	1.11	
	E <sub>M</sub>	0	.2	.8	1.7	4.1	6.1	7.8	20.7			
	E <sub>O</sub>	.0	.2	.8	1.7	4.2	6.4	7.4	20.7			
1951-57	D	0	0	1	3	7	8	12	31	1.09	1.11	
	E <sub>M</sub>	.0	1	7	2.0	4.8	10.9	9.8	28.4			
	E <sub>O</sub>	.0	1	7	2.1	5.0	11.0	9.2	28.0			
All calendar years	D	1	7	7	16	27	28	21	107			
	E <sub>M</sub>	.6	2.5	5.2	11.0	20.9	29.0	23.7	92.9			
	E <sub>O</sub>	4	2.1	5.2	11.4	22.9	30.7	22.3	93.2			
All calendar years	D/E <sub>M</sub>		2.83	1.33	1.46	1.29	.97	.88	1.15			
	D/E <sub>O</sub>		3.36	1.34	1.41	1.18	.91	.93	1.12			

Note Included as NOT OPERATED are

- 41 male and 6 female deaths occurring postoperatively after an ulcer operation;
- 25 male and 4 female deaths occurring in patients operated for cancer of the stomach or duodenum.

rates the mortality ratios are 1.67 for unoperated and 1.55 for operated males. For females the ratios are 1.19 and 1.15. On the whole, mortality ratios appear to decline with increasing age and with time. It should be born in mind, however that age and calendar year are associated, in that the young age groups contribute their observation years primarily to the early periods.

Use of Oslo death rates as a basis gives higher mortality ratios at ages 20-29 and 30-39 for both sexes. For ages 40-79 however the ratios on the Oslo basis are lower and markedly so in the case of males, than ratios on a Norwegian basis. At age 80 and over the relationship between the two ratios is irregular. For all ages combined the Oslo basis leads to lower ratios for males in all calendar year periods. For females too most of the calendar year periods, as well as the total for all years, show a reduction, but the differences are smaller than for males.

Time from the start of the observation period has not been accounted for in Table 4. The last three calendar year periods in the unoperated group do not contain any observation years immediately following discharge, these being years which may have a special mortality risk. In Table 5 account is taken of time from discharge, or time from operation, in conjunction with an analysis by site of ulcer and type of operation. On the other hand, all ages and all calendar years have been pooled in Tables 5 and 6.

Among unoperated patients the mortality ratio is higher for gastric than for duodenal ulcer. This is true for both sexes and for all periods after discharge. However the difference is not large. Males have higher ratios than females for both ulcer types. We note further that for unoperated patients the ratio is larger during the first 5 years after discharge than in later years.

For operated patients the ratios do not fall into a clear pattern, possibly because the numbers are small in some of the groups. The sexes are more equal than for unoperated patients, and there is no systematic difference between the two ulcer types or between the two operation types.

It may be of interest to compare these data with the Impairment Study of 1951 by the Society of Actuaries (4). A summary of their findings for ulcer patients is presented in Table 7. The investigation covered Ordinary insurance issued during the years 1935 through 1949 traced to policy anniversaries in 1950. Policies issued without medical examination were excluded as far as possible. Expected deaths and mortality ratios were based on the intercompany experience under standard medically examined Ordinary issues of 1935-49 traced to anniversaries in 1950-96. 60% of the included ulcer patients were males. Because few policies were issued to persons who had an active ulcer within the last two years, Table 7 has been limited to policy holders with one or more attacks within 3-10 years of application.

Comparison with data from the present study may be hazardous. Nevertheless, it is striking that Table 7 in contradistinction to Table 6 shows much higher mortality ratios for operated than for unoperated patients. Also Table 7 shows nearly the same ratios for gastric as for duodenal ulcers in unoperated patients.

Table 5

Actual deaths (D) from all causes and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by sex, ulcer site, type of operation, and years from discharge or operation

		MALES Years from discharge or operation				FEMALES Years from discharge or operation			
		0-4	5-14	15+	All years	0-4	5-14	15+	All years
<b>NOT OPERATED</b>									
Gastric ulcer	D	92	86	120	298	55	76	118	249
	$E_N$	90.9	50.6	79.9	161.4	33.5	69.1	99.0	201.6
	$E_O$	57.8	65.2	97.9	201.0	32.0	71.1	99.9	203.0
Duodenal ulcer	D	60	63	67	192	17	29	26	72
	$E_N$	30.8	52.7	48.6	132.1	13.3	31.1	24.8	69.2
	$E_O$	36.8	63.1	59.4	159.3	13.8	31.5	24.6	69.9
<b>OPERATED</b>									
Gastric ulcer Resection	D	11	11	12	34	5	9	8	20
	$E_N$	4.8	10.9	10.5	26.1	2.9	6.6	4.8	14.3
	$E_O$	5.9	14.0	12.9	32.8	3.0	8.8	4.9	14.5
Gastro- jejunostomy	D	8	12	15	35	1	4	5	8
	$E_N$	3.9	7.1	10.2	20.6	.8	1.5	3.6	5.9
	$E_O$	4.1	8.6	12.4	25.1	.8	1.6	3.7	6.1
Both operations	D	19	23	27	69	4	15	11	28
	$E_N$	8.1	17.9	20.7	46.7	3.6	11.1	8.5	20.2
	$E_O$	10.0	22.6	25.3	57.9	5.8	8.1	8.6	20.6
Duodenal ulcer Resection	D	16	45	26	87	5	9	6	20
	$E_N$	15.4	29.2	17.5	62.2	2.2	4.4	4.1	10.8
	$E_O$	17.5	33.3	22.0	75.0	2.2	4.6	4.2	11.0
Gastro- jejunostomy	D	16	51	69	140	4	6	18	28
	$E_N$	13.1	27.9	47.2	88.2	2.7	7.7	16.9	27.3
	$E_O$	16.4	35.4	58.4	110.2	3.0	11.1	17.0	28.3
Both operations	D	32	100	95	227	9	15	24	48
	$E_N$	28.5	57.1	64.7	150.4	4.9	12.1	21.0	38.1
	$E_O$	33.9	70.8	80.4	185.1	5.2	12.9	21.1	39.2

Table 6

Mortality ratios based on data in Table 5

	MALES				FEMALES			
	Years from discharge or operation				Years from discharge or operation			
	0-4	5-14	15+	All years	0-4	5-14	15+	All years
D/E <sub>N</sub> (Ratios based on Norwegian death rates)								
NOT OPERATED								
Gastric ulcer	2.93	1.70	1.50	1.85	1.64	1.10	1.19	1.23
Duodenal ulcer	1.95	1.23	1.38	1.45	1.28	.93	1.05	1.04
OPERATED								
Gastric ulcer								
Resection	2.29	1.01	1.14	1.30	1.03	1.36	1.67	1.40
Gastrojejunostomy	2.42	1.69	1.47	1.70		2.67	.83	1.36
Both operations	2.35	1.28	1.30	1.48	1.11	1.60	1.29	1.39
Duodenal ulcer								
Resection	1.04	1.54	1.49	1.40	2.27	2.05	1.46	1.85
Gastrojejunostomy	1.22	1.97	1.46	1.59	1.48	.78	1.07	1.03
Both operations	1.12	1.75	1.47	1.51	1.84	1.24	1.14	1.26
D/E <sub>O</sub> (Ratios based on Oslo death rates)								
NOT OPERATED								
Gastric ulcer	2.43	1.32	1.23	1.48	1.72	1.07	1.18	1.23
Duodenal ulcer	1.63	1.03	1.13	1.21	1.24	.92	1.03	1.03
OPERATED								
Gastric ulcer								
Resection	1.86	.79	.93	1.04	1.00	1.36	1.63	1.38
Gastrojejunostomy	1.95	1.40	1.21	1.59		2.50	.81	1.31
Both operations	1.90	1.02	1.07	1.19	1.05	1.49	1.28	1.36
Duodenal ulcer								
Resection	.91	1.27	1.18	1.16	2.27	1.96	1.43	1.82
Gastrojejunostomy	.98	1.55	1.18	1.27	1.33	.72	1.06	.99
Both operations	.94	1.41	1.18	1.23	1.73	1.16	1.14	1.22

Table 7

Summary mortality ratios from Impairment Study of 1951

Peptic ulcer: one or more attacks within 3-10 years of application, with or without haemorrhage	Standard policies	Substandard policies
NOT OPERATED		
Gastric	.98 ( $\pm .08$ )	1.21 ( $\pm .09$ )
Duodenal	.95 ( $\pm .04$ )	1.18 ( $\pm .06$ )
OPERATED		
Gastric	2.17 ( $\pm .18$ )	1.83 ( $\pm .12$ )
Duodenal	1.64 ( $\pm .10$ )	2.05 ( $\pm .13$ )

Figures in parentheses indicate approximate 50% confidence interval for ratios.

# MORTALITY BY CAUSE

Table 8 presents observed and expected deaths in the total material, using Norwegian mortality experience as a basis for comparison. Observed deaths are distributed both according to the official code and according to the revised code. In Table 9 are given differences and ratios between actual and expected deaths for both sexes combined.

The causes which show the largest and the smallest *differences* in Table 9 are

## NOT OPERATED

	Excess
Gastro-duodenal ulcer	+ 81.7
Cancer of stomach	+ 33.1
Pneumonia	+ 24.5
Coronary heart disease	+ 16.3
Valvular heart disease	+ 13.9

## OPERATED

Gastro-duodenal ulcer	+ 23.6
Pneumonia	+ 23.3
Tuberculosis of respiratory system	+ 19.7
Coronary heart disease	+ 15.6
Cancer of stomach	+ 11.3

## Deficit

Other dis. of cardiovascular system	- 16.3
Scillity	- 14.3
Diabetes mellitus	- 4.1
Compl. of pregnancy	- 1.8
Bronchitis and asthma	- 1.4

Scillity	- 8.2
Apoplexy	- 6.6
Other and unknown causes	- 3.0
Diabetes mellitus	- 2.5
Other dis. of respiratory organs	- 1.6

The causes which show the highest and the smallest *ratios* in Table 9 are (ignoring causes with expected number  $E_{\text{v}}$  less than 1.0 and bracketing ratios based on less than 5.0 expected deaths)

## NOT OPERATED

	High ratio
Gastro-duodenal ulcer	18.4
Cirrhosis of liver	( 5.7)
Cancer of lung	( 4.3)
Syphilis	( 3.5)
Leukemia and alucakemia	( 3.3)

## OPERATED

Gastro-duodenal ulcer	(8.0)
Other dis. of digestive organs	(4.9)
Dis. of bile ducts	(4.4)
Cancer of lung	(4.3)
Cirrhosis of liver	(4.0)

## Low ratio

Compl. of pregnancy	( 0)
Diabetes mellitus	4
Scillity	.6
Other dis. of cardiovascular system	7

Scillity	2
Diabetes mellitus	( 3)
Other dis. of respiratory organs	( 4)
Appendicitis	( 7)

Some of the observed departure from expectancy may be attributed to the fact that all the patients were originally living in Oslo, so that expected numbers based on Norwegian mortality experience may not be wholly appropriate. For observation years in the period 1951-7 it has been possible to compute expected numbers based on both Norwegian and Oslo mortality. The results are shown in Table 10, which also gives the ratio between expected number of deaths based on Oslo mortality and expected number of deaths based on Norwegian mortality. The ratios are strictly valid only for the period 1951-7. However they give an indication of the extent to which the ratios in Table 9 covering the years 1917-57 should be modified. Wherever the ratio  $E_{\text{O}}/E_{\text{v}}$  in

Table 4

rates reported in case of coronary mortality ( $E_{99}$ ) and actual deaths as well as  $M$  (all  $D_{10}$ ) and according to revised code  $D_{10}$  for the cause groups defined in Appendix II, by operation status and sex

	NOT OPERATED						OPERATED					
	Males			Females			Males			Females		
	Males and Females			Males and Females			Males and Females			Males and Females		
	$E_N$	$D_{10}$	$D_{95}$	$E_N$	$D_{10}$	$D_{95}$	$E_N$	$D_{10}$	$D_{95}$	$E_N$	$D_{10}$	$D_{95}$
in the 4 of respiratory system	26.9	31	17.7	3.5	3	4	44.5	46	45	18.0	20	20
in the 4 of tuberculosis	4.0	3	2.2	0.9	1	1	0.5	3	4	2.7	2	2
in the 4 of cancer and parasitic	2.0	0	1.0	0.5	1	1	1.1	1	1	0.4	0	0
in the 4 of cancer and parasitic	1.4	2	0	0	0	0	0	0	0	0	0	0
in the 4 of cancer and parasitic	4.9	5	3.5	1.1	1	1	8.1	8	6	3.4	0	0
in the 4 of cancer and parasitic	2.1	4	1.5	0.9	1	1	1.0	5	3	1.5	1	2
in the 4 of cancer and parasitic	23.3	50	10.0	2.5	25	25	39.9	73	100	17.1	25	21
in the 4 of cancer and parasitic	9.4	17	8.7	9	11	10.1	10.1	20	20	7.4	0	0
in the 4 of cancer and parasitic	4	0	0	0	0	0	0	0	0	0	0	0
in the 4 of cancer and parasitic	4	2	2	1	1	1	1	1	1	1	1	1
in the 4 of cancer and parasitic	2.3	9	1.1	0.5	2	2	3.2	14	17	2.2	2	2
in the 4 of cancer and parasitic	1.5	4	0.9	0.4	4	4	2.4	8	8	1.4	3	2
in the 4 of cancer and parasitic	10.1	24	25.1	30	37	41.3	54	60	12.0	16	10	10
in the 4 of cancer and parasitic	2.9	2	1	0	1	1	1	1	1	2	1	1
in the 4 of cancer and parasitic	0	1	0	0	1	1	0	2	2	0	0	0
in the 4 of cancer and parasitic	3	0	0	0	0	0	1	0	0	0	0	0
in the 4 of cancer and parasitic	30.9	35	37	41.8	40	57	72.7	85	91	22.5	16	14
in the 4 of cancer and parasitic	31.5	45	47	42	27	2	53.7	72	70	24.0	41	40
in the 4 of cancer and parasitic	11.8	20	9	14.4	20	30	26.1	40	39	9.1	12	11
in the 4 of cancer and parasitic	20.0	15	10	25.5	15	27	40.2	30	45	14.0	10	10
in the 4 of cancer and parasitic	8.1	10	15	4.7	7	5	17.7	25	20	0.5	3	3
in the 4 of cancer and parasitic	18.2	30	31	22.5	29	26	40.5	85	65	11.0	20	24
in the 4 of cancer and parasitic	3.0	4	5	4.5	5	2	6.4	7	7	2.8	4	6
in the 4 of cancer and parasitic	2.9	7	4	1.5	6	5	4.3	13	7	2.2	1	1
in the 4 of cancer and parasitic	3.8	60	20	1.5	27	25	7.5	07	05	2.1	25	14
in the 4 of cancer and parasitic	1.1	0	1.4	2	5	2	2.6	5	4	0	4	1

Table 8 (cont.)

	NOT OPERATED						OPERATED					
	Males			Females			Males			Females		
	E <sub>x</sub>	D <sub>o</sub>	D <sub>x</sub>	E <sub>y</sub>	D <sub>o</sub>	D <sub>x</sub>	E <sub>x</sub>	D <sub>o</sub>	D <sub>x</sub>	E <sub>y</sub>	D <sub>o</sub>	D <sub>x</sub>
27 Pleur and hernia	28	5	6	3.0	1	3.8	6	7	5	1.9	3	5
28 Appendicitis	1.6	5	4	.8	2	1	2.4	7	5	1.1	1	1
29 Cirrhosis of liver	1.2	6	9	7	3	6	1.9	11	13	1.0	3	3
30 Diseases of bile ducts	9	2	1	2.1	4	2	3.0	6	3	7	2	2
31 Other diseases of digestive org.	2.5	7	5	2.7	4	4	4.7	11	11	1.8	11	11
32 Nephritis	8.4	12	8	6.1	8	4	14.5	20	12	3.9	12	3.9
33 Other diseases of urinary org.	8.6	12	13	2.5	5	5	11.2	17	18	5.7	3	3
34 Complications of pregnancy	11	1	1	1.8	0	1	1.8	0	1	-	-	-
35 Diseases of skin, cellular tissue, bones, and org. of movement	10.8	10	10	1.5	1	1	2.8	2	2	0	0	0
36 Semilly	4.7	13	15	9	11	11	31.5	21	21	5.7	1	1
37 Suicide	28.3	31	36	7.0	3	3	3.6	16	18	3.9	12	14
38 Accidents and homicides	19.7	52	25	18.1	16	16	35.3	59	43	21.2	30	30
39 Other and unknown causes	32.3	7	34	297.5	35	35	37.9	48	41	14.5	12	14
All causes	323	7	34	297.5	35	35	621.2	805	80	237.2	368	92.9
										107	107	530 d
										473	473	473



Table 9

Difference and ratio between actual deaths according to official cod ( $D_0$ ) and deaths expected on basis of Norwegian mortality ( $E_0$ ) for the cause groups defined in Appendix II

Total material by operation status, males and females combined

In parentheses Ratios based on expected numbers smaller than 5

Ratios not computed where expected number is smaller than 1

	$D_0 - E_0$		$D_0/E_0$	
	Not operated	Operated	Not operated	Operated
1 Tuberculosis of resp. system	+ 1.5	+ 19.7	1.0	1.9
2 Other forms of tuberculosis	— 1.3	— .2	.8	(.9)
3 Syphilis	+ 8.6	+ 7	(3.5)	(1.5)
4 Influenza	— .3	— .2	(.9)	(.8)
5 Other infectious and parasitic diseases	— 1	+ 2.7	1.0	(1.6)
6 Cancer of oesophagus	+ 2.0	+ 2.2	(1.7)	(2.2)
7 Cancer of stomach	+ 35.1	+ 11.3	1.9	1.5
8. Other cancers of digestive organs	+ 7.9	— 1.3	1.4	.9
9 Cancer of pharynx	— .6	+ 2.6		
10 Cancer of larynx	+ 2.5	+ 1.7		
11 Cancer of lung	+ 10.8	+ 8.4	(4.3)	(4.3)
12 Leukaemia and aleukaemia	+ 5.6	+ 2.3	(3.3)	(2.4)
13. All other malignant tumours	+ 12.7	+ 6.7	1.3	1.3
14 Diabetes mellitus	— 4.1	— 2.5	.4	(.3)
15. Psychoses	+ 4	— .9	(1.2)	
16. Chronic alcoholism	— .3	+ .8		
17 Apoplexy	+ 12.3	— 6.6	1.2	.8
18. Coronary heart disease	+ 16.3	+ 15.6	1.3	1.4
19 Valvular heart disease	+ 13.9	+ 3.4	1.5	1.3
20 Other diseases of cardio-vascular system	— 16.2	— 1.3	.7	.9
21 Sudden death - heart paralysis	+ 9.3	+ 3.0	1.7	1.4
22. Pneumonia	+ 24.5	+ 23.2	1.6	2.2
23. Bronchitis and asthma	— 1.4	+ .8	.8	(1.2)
24 Other dis. of respiratory organs	+ 8.7	— 1.6	(3.0)	(.4)
25. Gastro-duodenal ulcer	+ 81.7	+ 23.6	16.4	(8.0)
26. Acute and chronic gastric catarrh	+ 2.4	+ .8	(2.0)	(1.7)
27. Ileus and hernia	+ .2	+ 3.1	1.0	(2.1)
28. Appendicitis	+ 4.6	— 4	(2.9)	(.7)
29. Cirrhosis of liver	+ 9.1	+ 3.8	(5.7)	(4.0)
30. Diseases of bile ducts and gall bladder	+ 3.0	+ 4.6	(2.0)	(4.4)
31. Other diseases of digestive organs	+ 6.3	+ 9.8	(2.3)	(4.9)
32. Nephritis	+ 3.5	+ 6.2	1.4	1.8
33. Other diseases of urinary and genital organs	+ 5.8	— 1.5	1.5	.8
34. Complications of pregnancy childbirth, and puerperium	— 1.8	— .3	(.0)	
35. Diseases of skin, cellular tissue, and of organs of movement	— .6	— .3	(.8)	(.8)
36. Senility	— 14.3	— 9.2	.6	.2
37. Suicide	+ 10.4	+ 7.8	2.8	(2.9)
38. Accidents and homicide	+ 3.7	+ 9.6	1.1	1.4
39. Other and unknown causes	+ 10.1	— 3.0	1.3	.8
All causes	+ 273.8	+ 145.0	1.44	1.44

Table 10

Observation years during period 1951-1957

Actual deaths according to official code ( $D_C$ ) and deaths expected on basis of Norwegian mortality ( $L_N$ ) and on basis of Oslo mortality ( $E_O$ ) with ratio between the two expectations, for cause groups defined in Appendix 11. Total material by operation status, males and females combined

	NOT OPERATED			OPERATED			$E_O/L_N$	
	$D_C$	$L_N$	$E_O$	$D_C$	$E_O$	$L_N$	Not oper	Oper
1 Tuberculosis of resp. system	4	2.1	2.3	3	2.0	2.3	1.07	1.15
2 Other forms of tuberculosis	1	.3	.3		.3	.2	.88	.79
3 Syphilis	4	.6	1.2		.5	1.1	2.10	2.04
4 Influenza	1	.3	1		.2	1	.23	.23
5 Other infect. and parasit. dis.	2	.5	.5	1	.4	.4	.98	.89
6 Cancer of oesophagus		.6	1.5		.5	1.3	2.31	2.47
7 Cancer of stomach	7	9.1	7.7	13	7.1	6.1	.85	.86
8 Other cancers of digest. organs	10	5.5	8.0	3	4.1	6.0	1.44	1.48
9 Cancer of pharynx		.2	.5	1	.2	.5	2.53	2.93
10 Cancer of larynx	1	1	.2		1	.2	.13	2.10
11 Cancer of lung	6	1.2	3.4	7	1.3	3.7	2.80	2.80
12 Leukaemia and leukaemia	3	1.0	1.4	2	.8	1.1	1.34	1.52
13 All other malignant tumours	19	13.5	13.5	14	8.9	10.6	1.15	1.19
14 Diabetes mellitus		1.3	1.2	1	.8	.9	.88	1.12
15 Psychoses		.6	.5		.4	.3	.81	.74
16 Chronic alcoholism		1	1		1	1	1.58	1.61
17 Apoplexy	27	25.0	25.3	12	15.6	16.6	1.01	1.07
18 Coronary heart disease	34	28.8	39.0	36	21.8	30.9	1.35	1.42
19 Valvular heart disease	3	3.2	3.4		2.1	2.3	1.07	1.09
20 Other dis. of cardio-vasc. s.	10	17.2	16.6	11	10.9	11.0	.97	1.01
21 Sudden death - heart paralysis	4	2.4	2.4	3	2.1	2.1	.99	.99
22 Pneumonia	9	6.8	9.6	4	4.1	6.1	1.42	1.49
23 Bronchitis and asthma		1.9	1.6	2	1.4	1.3	.85	.96
24 Other dis. of respiratory organs	1	1.0	1.4		.8	1.2	1.40	1.48
25 Gastro-duodenal ulcer	7	.9	1.3	3	.8	1.2	1.54	1.60
26 Ac. and chr. gastric catarrh	1	.3	.2		.2	1	.76	.71
27 Ileus and hernia	1	1.1	1.0	1	.7	.6	.92	.92
28 Appendicitis		.2	.2	1	.2	.2	1.12	1.05
29 Cirrhosis of liver	5	.7	1.9	2	.5	1.5	2.69	2.75
30 Dis. of bile ducts and gall bl.	1	.9	1.2	3	.3	.8	1.36	1.50
31 Other dis. of digestive organs	1	.7	1.0	1	.5	.7	1.36	1.99
32 Nephritis	2	1.7	1.6	1	1.4	1.3	.91	.91
33 Other dis. of urinary org.	3	2.9	2.8	1	2.2	2.2	.98	.96
34 Complications of pregnancy		.0	.0		.0	.0	.42	.40
35 Diseases of skin		.6	.6	1	.4	.3	.89	.91
36 Scellity	3	5.6	1.1	1	2.9	.6	.21	.19
37 Suicide	3	1.2	1.6	1	1.3	1.7	1.32	1.30
38 Accidents and homicide	7	5.8	6.2	2	5.0	5.0	1.06	1.00
39 Other and unknown causes	8	6.7	5.2	3	4.8	4.1	.78	.84
All causes	192	132.4	169.4	134	107.9	126.6	1.11	1.17

Table 10 is about the same as the ratio  $D_C/E_T$  in Table 9 one would suspect that any excess or deficit in Table 9 could be ascribed to a biased expectancy.

It can be seen that for causes such as cancer of oesophagus, coronary heart disease, and senility the entire deviation in Table 9 might well be eliminated if Oslo mortality were to be used as a basis for comparison. For other causes the use of an Oslo basis would reduce the difference between actual and expected deaths, but would hardly remove it entirely. This seems to be the case with cancer of lung, leukaemia, cirrhosis of liver and suicide. The excess of deaths from cancer of the stomach might be slightly increased by the use of Oslo mortality for comparison.

There were 133 deaths among patients who had a perforating gastric or duodenal ulcer at the start of observation. Expected numbers of death were not computed separately for this group. However the cause-of-death distribution showed no significant differences from the distribution of the remaining 1,257 deaths.

The more important causes of death will now be discussed individually in connection with a break-down by site of ulcer, type of operation, and time from the start of observation.

#### TUBERCULOSIS OF RESPIRATORY SYSTEM

Table 11 shows actual deaths and deaths expected on the basis of Norwegian mortality by site of ulcer, type of operation, and duration of observation.

There is no evidence of abnormal mortality among unoperated duodenal ulcer patients. For unoperated gastric ulcer patients the data for both sexes, all years after discharge, show only a slight excess mortality. The pooled data, however, conceal a very considerable excess, particularly in males, for the observation years which follow 15 or more years after discharge.

In connection with this contrast between unoperated gastric and duodenal ulcers, it may be noted that in British mortality and morbidity statistics, summarized by Susser & Stem (5) the social class distribution is different for the two types of ulcer. The ratio between gastric and duodenal ulcer rates increases from social group I to V. In Northern Norway Schanke (6) found that the ratio between gastric and duodenal ulcers was much larger in fishermen than in men of other occupations. No analysis by occupation or social class has been made in the present material, however.

Among operated patients there is an excess mortality which seems to be roughly the same for both sexes, both ulcer sites, and both operation types. Of course the numbers are too small for any definite statement to be made about the relative risks.

It is noteworthy that neither for unoperated nor for operated patients is there any sign of excess mortality in the first 5 years of the observation period. Of the 14 patients for whom tuberculosis or infiltration of the lungs was mentioned as a discharge diagnosis in addition to ulcer (Appendix I i) only one is included among the deaths in Table 11.

Age and calendar year period are taken into account in Table 12.

Table 11

## Tuberculous of respiratory system

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Normal mortality ( $E_N$ ) by sex, operation status, site of ulcer type of operation, and years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15+			All years		
	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	4.9	2	2	5.0	7	8	2.7	12	12	12.5	21	22
Females	5.0	3	3	5.4	2	2	4	5	5	12.8	10	10
M + F	9.9	5	5	10.3	9	10	5.1	17	17	25.3	31	32
Duodenal ulcer												
Males	5.2	3	4	4.9	2	2	1.5	2	1	11.6	9	7
Females	1.6			1.5	4	4	4			3.4	4	4
M + F	6.8	3	4	6.3	6	6	1.9	2	1	15.0	13	11
<b>OPERATED</b>												
Gastric ulcer												
Resection												
Males	.6	1	1	7	2	3	.3	1	1	1.6	4	5
Females	.3			.2	1	1	1			.6	1	1
M + F	.9	1	1	9	3	4	.3	1	1	2.2	5	6
Gastrojejunostomy												
Males	.6	1	1	.6	2	2	.3			1.5	3	3
Females	1			1	2	2	1			4	2	2
M + F	7	1	1	.8	4	4	4			1.9	5	5
Both operations												
Males	1.2	2	2	1.3	4	5	.6	1	1	3.1	7	8
Females	4			4	3	3	1			.9	3	3
M + F	1.6	2	2	1.7	7	8	7	1	1	4.0	10	11
Duodenal ulcer												
Resection												
Males	2.4	1	1	2.6	3	5	7	1	2	5.7	7	8
Females	4	1	1	.3	1	1	1			.8	2	2
M + F	2.8	2	2	2.9	6	6	.8	1	2	6.5	9	10
Gastrojejunostomy												
Males	2.3	2	2	2.8	7	7	1.7	7	7	6.9	15	16
Females	.3			4			.2	1	1	1.0	1	1
M + F	2.7	2	2	3.2	7	7	1.9	8	8	7.9	17	17
Both operations												
Males	4.7	3	3	5.4	12	12	2.4	8	9	12.6	23	24
Females	7	1	1	7	1	1	.3	1	1	1.7	3	3
M + F	3.4	4	4	6.1	13	13	2.7	9	10	14.3	26	27

Table 12

## Tuberculosis of respiratory system

Calendar year period 1941-57

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by sex, age, operation status, and site of ulcer

	Age attained											
	Under 50				50 and over				All ages			
	$E_N$	$E_O$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	1.4	1.6	3	3	2.2	2.9	11	11	3.6	4.4	14	14
Females	.9	.6			1.4	1.0	5	5	2.2	1.6	5	5
M + F	2.3	2.1	3	3	3.3	3.9	16	16	5.8	6.0	19	19
Duodenal ulcer												
Males	3.2	3.2	1	1	2.0	2.6	3	2	5.1	5.8	4	3
Females	.8	.5			.6	.4	2	2	1.4	.9	2	2
M + F	3.9	3.7	1	1	2.6	3.1	5	4	6.5	6.7	6	5
<b>OPERATED</b>												
Gastric ulcer												
Males	.7	.7	2	2	.8	1.1	2	2	1.5	1.8	4	4
Females	1	1	1	1	.2	.2			.3	.2	1	1
M + F	.8	.9	3	3	1.1	1.3	2	2	1.8	2.1	5	5
Duodenal ulcer												
Males	1.2	3.4	4	6	2.6	3.4	8	8	3.8	6.8	12	14
Females	.3	.2			.3	.2	2	2	.6	.4	2	2
M + F	3.5	3.6	4	6	2.9	3.6	10	10	6.4	7.2	14	16

The excess mortality of unoperated gastric ulcer patients is seen to be limited to age 50 and above. Operated patients show an indication of excess mortality in both age groups.

A further subdivision of the period 1941-57 is presented in Table 13. This table gives expected deaths based on both Norwegian and Oslo mortality.

It appears that the excess mortality of unoperated gastric ulcer patients in the period 1941-57 is not limited to the war years 1941-5. In fact, the mortality ratio is higher in the post war years.

The basis for cause of death in the III deaths according to the revised code in Table 11 was as follows:

	Not operated	Operated	Total
Autopsy	18	12	30
Diagnosed in hospital or by Health Department prior to death	22	19	41
No information in addition = death certificate	3	7	10
	43	38	81

Table 13

## Tuberculosis of respiratory system

Actual deaths according to official code ( $D_O$ ), deaths expected on basis of Norwegian mortality ( $E_N$ ) and deaths expected on basis of Oslo mortality ( $E_O$ ) by operation status and site of ulcer for the calendar year periods 1941-45, 1946-50, and 1951-57. Both sexes, all ages combined

		Calendar year periods			
		1941-45	1946-50	1951-57	1941-57
<b>NOT OPERATED</b>					
Gastric ulcer	$D_O$	7	9	3	19
	$E_N$	3.1	1.8	1.0	3.8
	$E_O$	3.2	1.8	1.0	6.0
Duodenal ulcer	$D_O$	3	2	1	6
	$E_N$	3.8	2.0	.9	6.5
	$E_O$	3.7	2.0	1.0	6.7
<b>OPERATED</b>					
Gastric ulcer	$D_O$	2	2	1	5
	$E_N$	.8	.6	.4	1.8
	$E_O$	.9	.7	.4	2.1
Duodenal ulcer	$D_O$	7	5	2	14
	$E_N$	2.9	2.3	1.3	6.4
	$E_O$	3.3	2.5	1.4	7.2

The association between ulcer and pulmonary tuberculosis is no new observation. For instance, in a retrospective study Holmboe & Nissen-Meyer (7) found an excess of both operated and unoperated peptic ulcers in tuberculosis patients as compared to patients with other lung diseases.

## OTHER FORMS OF TUBERCULOSIS

The findings for this group are shown by site of ulcer in Table 14. There is no sign of any excess mortality which may be contrasted with the findings for tuberculosis of the respiratory system.

Table 14

## Other forms of tuberculosis

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status, site of ulcer and calendar year period

For the period 1941-57. Deaths expected on basis of Oslo mortality ( $E_O$ )

		Calendar year period						
		1917-37			1941-57			
		$E_N$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$
NOT OPERATED								
Gastric ulcer		3.4	3	2	7	.5	2	1
Duodenal ulcer		2.2	2	2	.9	.5	0	0
OPERATED								
Gastric ulcer		.6	0	0	.2	1	0	0
Duodenal ulcer		2.1	1	1	.8	.3	1	1

As shown there were 5 deaths ascribed to this cause in the revised code. Autopsy was performed in 4 cases, whereas the diagnosis was made in hospital without autopsy in the remaining case.

## SYPHILIS

Table 15 shows an excess mortality among gastric ulcer patients.

Table 15

### Syphilis

Actual deaths according to official code ( $D_0$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status, site of ulcer and years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$
NOT OPERATED												
Gastric ulcer	.3		1	.6	2	5	.8	5	6	1.8	7	12
Duodenal ulcer	.3			.6	1	1	4	2		1.3	3	1
OPERATED												
Gastric ulcer	1	1	1	.2		1	1			4	1	2
Duodenal ulcer	.3			.6		1	.5	1	1	1.4	1	2

From Table 10 it can be seen that in 1951-7 the Oslo mortality was about twice the Norwegian mortality from syphilis. Part of the excess among gastric ulcer patients might accordingly be explained by bias in the expected number of deaths. However the striking contrast between gastric and duodenal ulcers will be largely unaffected by this bias. Possibly the data can be interpreted as supporting the suggestion made in connection with tuberculosis of the respiratory system that the social class distribution is different for gastric and duodenal ulcers.

Four of the 17 patients in Table 15 who died from syphilis according to the revised code had signs of cardiovascular or central nervous system syphilis at the start of the observation period. One patient had a history of treatment for syphilis and one had a positive serological reaction. In the remaining cases there was no mention of syphilis in the hospital record at the start of observation, and serological tests for syphilis were not made.

Of the 17 deaths 11 were ascribed to cardiovascular and 6 to central nervous system syphilis. Autopsy was performed in 10 cases. Five other patients died in hospital. In the remaining 2 cases cardiovascular syphilis had been diagnosed in hospital prior to death.

## CANCER OF OESOPHAGUS

The difference between Oslo and Norwegian mortality is large for this cause. This is illustrated by the difference in the two expectancies for the period 1941-57 in Table 16

Table 16  
*Cancer of oesophagus*  
 Actual deaths according to official code (Dc) and according to revised code (Da) and deaths expected on basis of Norwegian mortality (E<sub>v</sub>) by operation status, site of ulcer and calendar year period  
 For the period 1941-57 Deaths expected on basis of Oslo mortality (E<sub>o</sub>)

	Calendar year period				1941-57			
	1917-57							
	E <sub>v</sub>	D <sub>c</sub>	D <sub>a</sub>		E <sub>v</sub>	E <sub>o</sub>	D <sub>c</sub>	D <sub>a</sub>
NOT OPERATED								
Gastric ulcer	17	4	3		9	10	1	1
Duodenal ulcer	10				7	17		
OPERATED								
Gastric ulcer	4	3	2		3	6	2	1
Duodenal ulcer	10				7	19		

Autopsy was performed in only one of the 5 deaths in Table 16 (revised code). In one other case the diagnosis was verified by biopsy. One patient had been treated in hospital for cancer of oesophagus on the basis of X-ray findings only. In the remaining 9 cases no information is available in addition to the death certificate.

There is no evidence of any abnormal mortality from this cause in the material.

#### CANCER OF STOMACH

In a material from Rikshospitalet, Oslo, Helungen & Hillertad (8) found more gastric cancers than expected on the basis of Norwegian mortality in patients who had had a resection for gastric ulcer. No excess was found if resection had been performed for duodenal ulcer. The interval between the resection and the diagnosis of cancer was on an average 20 years. Laavaag (9) in a similar follow up of patients resected in Drammen Hospital in 1932-45 found very nearly the expected number of gastric cancer deaths both in gastric and duodenal ulcer patients. He concludes that in patients operated upon for gastric ulcer the cancer incidence in residual stomach is reduced to an extent which approaches the incidence in the general population, but in the duodenal ulcer group cancer incidence increases to an extent that also approaches the rate for the general population.

Data from the present material are presented in Table 17 by sex, site of ulcer operation type, and years from start of observation.

During the first 5 years after discharge there is a very heavy excess mortality among unoperated gastric ulcer patients. For duodenal ulcers the excess is much smaller.

It is reasonable to assume that most of the deaths during the first 5 years after discharge represent errors of diagnosis, i.e. that the cancer was in fact present at the start of the observation period. This view is supported by the



Table 17

## Cancer of stomach

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_M$ ) by sex, operation status, site of ulcer type of operation, and years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	$E_M$	$D_O$	$D_R$	$E_M$	$D_O$	$D_R$	$E_M$	$D_O$	$D_R$	$E_M$	$D_O$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	2.1	25	26	4.1	8	7	6.0	8	9	12.2	39	42
Females	1.9	9	10	4.1	6	6	3.4	3	3	11.4	18	19
M + F	4.0	34	36	8.2	12	13	21.3	11	12	23.5	57	61
Duodenal ulcer												
Males	1.8	5	5	3.7			3.5	2	2	9.0	7	7
Females	.8	2	2	1.8			1.3	2	1	3.8	4	3
M + F	2.6	7	7	5.4			4.8	4	3	12.8	11	10
<b>OPERATED</b>												
Gastric ulcer												
Resection												
Males	.3			.9			.8			2.0		
Females	.2			.4	2	2	.3	1	1	.8	3	3
M + F	.5			1.2	2	2	1.1	1	1	2.8	3	3
Gastrojejunostomy												
Males	.2	2	1	.5	1		.7	3	2	1.4	6	3
Females	.0			.1			.2			.4		
M + F	.3	2	1	.6	1		.9	3	2	1.8	6	3
Both operations												
Males	.6	2	1	1.4	1		1.5	3	2	3.4	6	3
Females	.2			.5	2	2	.5	1	1	1.2	3	3
M + F	.8	2	1	1.9	3	2	2.0	4	3	4.7	9	6
Duodenal ulcer												
Resection												
Males	.8			1.9	1	1	1.5			4.0	1	1
Females	.1			.3			.2			.6		
M + F	.9			2.2	1	1	1.5			4.6	1	1
Gastrojejunostomy												
Males	.9	2	2	2.2	3	4	3.6	8	5	6.7	11	11
Females	.2			.6	1	1	.9	3	2	1.6	4	3
M + F	1.1	2	2	2.7	4	5	4.5	11	7	8.3	15	14
Both operations												
Males	1.7	2	2	4.1	4	5	4.9	6	5	10.7	12	12
Females	.3			.8	1	1	1.1	3	2	2.3	4	3
M + F	2.0	2	2	4.9	5	6	6.0	9	7	13.0	16	15
Both sites, both sexes												
Resection	1.4			3.4	3	3	2.6	1	1	7.5	4	4
Gastrojejunostomy	1.4	4	5	3.3	5	5	5.4	12	9	10.2	21	17
Both operations	2.8	4	5	6.8	8	8	8.0	13	10	17.6	25	21

following summary of the X ray examinations during the registered stay of the unoperated patients who died from stomach cancer during the first 5 years

X-ray during stay	Discharge diagnosis Gastric ulcer	Duodenal ulcer
Negative	9	2
Doubtful ulcer	7	
Definite ulcer	8	1
Not examined	12	4
	36	7

We note, however that even the 8 gastric ulcer patients who had the diagnosis made by X ray (without indication of malignancy) exceed the expected number (40) of cancer deaths. Also Table 18 is noteworthy in this connection. It shows that the excess cancer mortality during the first 5 years after discharge remained practically the same throughout the period of registration (1917-39) despite the great increase in utilization of X-ray (Appendix I b)

Table 18

Cancer of stomach  
Mortality in unoperated patients during first 5 years after discharge  
Actual deaths according to official code (D<sub>c</sub>) and deaths expected on basis of Norwegian mortality (E<sub>v</sub>) by site of ulcer and calendar year period

	1917-26		1927-30		1931-35		1936-40		1941-45	
	E <sub>v</sub>	D <sub>c</sub>	E <sub>v</sub>	D <sub>c</sub>	E <sub>v</sub>	D <sub>c</sub>	E <sub>v</sub>	D <sub>c</sub>	E <sub>v</sub>	D <sub>c</sub>
Gastric ulcer	1.3	1.2	.6	.8	.8	.4	1.0	.6	.3	.4
Duodenal ulcer	.2	1	.2	2	.6	1	1.2	2	4	1

Table 17 shows that when more than 5 years have passed after discharge, unoperated gastric ulcer patients have a practically normal stomach cancer mortality risk. For duodenal ulcer patients the actual deaths are remarkably few suggesting that a (correct) diagnosis of duodenal ulcer implies a reduced stomach cancer risk.

For operated patients it is noteworthy that actual deaths are fewer than expected among resected patients. In all 4 cases in Table 17 the resection had been performed according to the Billroth II method. In 2 cases the resection was described as subtotal.

Gastrojejunostomies show the opposite tendency there are more stomach cancer deaths than expected. The excess is not limited to the first 5 years after operation. It is particularly noteworthy that there is no apparent difference between gastric and duodenal ulcers where gastrojejunostomy has been performed. Eliminating the first 5 years after discharge or operation the data can be summarized as follows

	$E_M$	Gastric			$E_M$	Duodenal		
		$D_C$	$D_R$			$D_C$	$D_R$	
Not operated	19.5	23	25		10.2	4	3	
Resection	2.3	3	3		9.7	1	1	
Gastrojejunostomy	1.5	4	2		7.2	13	12	

As far as is known, none of the patients who had a gastrojejunostomy had later been resected for peptic ulcer.

It may be noted that of the 15 deaths in Table 17 among operated duodenal ulcer patients 5 occurred in patients whose ulcer had been situated in the pylorus and 10 in patients with the ulcer in the duodenum proper.

Table 19 gives a break-down by age and calendar year period. The first 5 years of the observation period have been excluded for both unoperated and operated. For the period 1941-57 expected numbers are given on both a Norwegian and an Oslo basis. The latter gives moderately smaller expectations.

Table 19

Cancer of stomach

Mortality more than 5 years after discharge/operation

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_M$ ) by site of ulcer, age, operation status, and calendar year period.

For the years 1941-57: Deaths expected on basis of Oslo mortality ( $E_O$ )

	NOT OPERATED								OPERATED							
	$E_M$	Gastric			Duodenal				$E_M$	Gastric			Duodenal			
		$E_O$	$D_C$	$D_R$	$E_M$	$E_O$	$D_C$	$D_R$		$E_O$	$D_C$	$D_R$	$E_M$	$E_O$	$D_C$	$D_R$
Age 20-59																
1917-40	2.1		3	3	.6				.3				.9		1	1
1941-57	2.3	2.3	5	5	2.3	2.1	1	1	8	7	1	1	.8	2.5	5	5
Age 60+																
1917-40	5.0		8	8	1.1				.6		2	1	1.6		2	2
1941-57	9.9	8.4	10	12	6.3	5.3	3	2	2.3	1.9	4	3	3.6	4.8	6	5
Age 0 and over																
1917-40	7.0		8	8	1.6				.9		2	1	2.3		3	3
1941-57	12.4	10.6	15	17	8.6	7.4	4	3	3.0	2.6	5	4	8.4	7.3	11	10
All years	19.5		23	25	10.2		4	3	3.9		7	5	10.9		14	13

There is no apparent difference between age groups or between calendar year periods.

The diagnostic basis for the 92 deaths in Table 17 (revised code) can be summarized as follows:

	NOT OPERATED		OPERATED	
	Gastric	Duodenal	Gastric	Duodenal
Autopsy	21	4	5	3
No autopsy but diagnosed at operation	20	3	1	4
No autopsy or operation				
Died in hospital	6			2
Diagnosed in hospital prior to death	2	1		2
Died at home. \ other information	12	2	2	4
	61	10	8	15

In addition to the 92 deaths in Table 17 the total material contained 18 deaths from cancer of the stomach. Nine of these occurred in unoperated patients where the discharge diagnosis at the start of observation indicated that the ulcer was doubtful. Malignancy was mentioned as a possibility in 5 cases. Of the 9 operated patients 5 had had a gastrojejunostomy. Either no ulcer was found or the description was inadequate for classification by site. As far as is known, none had later had a resection for peptic ulcer. Three deaths occurred in the first 5 years after operation, one after 17 years, and one after 37 years. Two patients had a Billroth I resection, with no definite ulcer described 4 and 5 years prior to death. One patient had a Polya resection, during which an ulcer was found in the stomach and in the duodenum, 14 years before death. Finally, one patient had a resectio circularis ventriculi for gastric ulcer 13 years prior to death.

Eleven patients in the material had an operation for cancer of the stomach, but were alive at the end of the observation period or died from other causes. One of these patients had previously had a gastrojejunostomy for his ulcer, one had had a resectio circularis ventriculi, while the remaining 9 patients had not been operated for their ulcer.

#### OTHER CANCERS OF DIGESTIVE ORGANS

Table 20 gives the data for both sexes combined.

It may be noted that 2 of the 5 deaths during the first 5 years after discharge are cases where the cancer was probably present at the start of observation causing an error of diagnosis. One was a duodenal cancer and the other was a primary hepatic cancer in a cirrhotic liver. Even allowing for these cases the actual deaths among unoperated patients exceed the number expected on a Norwegian basis. It should be noted however that in 1951-7 the number expected on the basis of Oslo mortality was about 40 % higher than the number expected on the basis of Norwegian mortality (Table 10).

For operated patients there is no suggestion of any abnormal mortality. The diagnosis in the 34 deaths according to the revised code was

	NOT OPERATED		OPERATED	
	Gastric	Duodenal	Gastric	Duodenal
Cancer of duodenum	1			
Cancer of colon	4	6		1
Cancer of rectum	3	3		1
Cancer of pancreas	2			2
Cancer of gall bladder	2			
Cancer of bile ducts		1		
Cancer of liver primary	1	1		
Cancer of intestines, with metastases to liver		1		
Cancer of liver unspecified	1	1	1	1
Abdominal tumour (Cancer of pancreas?)			1	
	14	13	2	5

The diagnostic basis for cause of death can be summarized as follows

Autopsy	21
No autopsy but diagnosed at operation	5
No autopsy or operation	
Definite clinical diagnosis	2
Died in hospital, but no other information	1
Died at home. No other information	5
	<hr/> 34

Table 20

Other cancers of digestive organs

Actual deaths according to official code ( $D_0$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status, type of operation, site of ulcer and years from discharge/operation

	Number of years after discharge/operation											
	0-4			5-14			15+			All years		
	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$
NOT OPERATED												
Gastric ulcer	1.3	3	3	3.2	3	2	6.0	7	9	10.5	13	14
Duodenal ulcer	.9	2	2	2.4	4	5	2.6	6	6	6.0	12	13
OPERATED												
Gastric ulcer												
Resection	.2			6	1	1	6		1	1.4	1	2
Gastrojejunostomy	1			.2			.5			.8		
Both operations	.3			.8	1	1	1.0		1	2.2	1	2
Duodenal ulcer												
Resection	4			1.1	1	1	.8			2.3	1	1
Gastrojejunostomy	.3			1.0			2.2	3	4	3.5	3	4
Both operations	7			2.1	1	1	3.0	3	4	5.8	4	5

#### CANCER OF PHARYNX AND CANCER OF LARYNX

These cancer types are presented together in Table 21

It should be remembered that in Oslo death rates for these conditions are much higher than for the country as a whole. For the period 1941-57 the

Table 21

## Cancer of pharynx and cancer of larynx

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status and site of ulcer

	Pharynx			Larynx			Pharynx and larynx		
	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$
NOT OPERATED									
Gastric ulcer	.3			.3	1	1	.6	1	1
Duodenal ulcer	.2		1	.2	2	2	.4	2	3
Both sites	.5		1	.5	3	3	.9	3	4
OPERATED									
Gastric ulcer	1			.0			1		
Duodenal ulcer	.2	2	2	.2	1	1	.4	3	3
Both sites	.3	2	2	.2	1	1	.5	3	3
NOT OPERATED and OPERATED									
Both sites	7	2	3	7	4	4	14	6	7

expected number of deaths from both cancer types combined was 1.0 based on Norwegian mortality and 2.5 based on Oslo mortality. Actual deaths were 5 both according to the official and the revised code.

The numbers are so small that this excess mortality does not mean much by itself. It should be seen in conjunction with the excess mortality from lung cancer.

All 3 pharynx cancer deaths in Table 21 were stated to be located in the hypopharynx. Two of the patients were females. Of the 4 larynx cancer patient 3 were males.

The cause of death is known to have been histologically verified for all the 7 deaths in Table 21.

## CANCER OF LUNG

Table 22 gives the data by site of ulcer, operation type, and years from start of operation, with both sexes combined.

There is a distinct excess mortality which seems to be of roughly the same magnitude for both sites and for both operated and unoperated patients. Time since discharge or operation appears to have little importance.

Oslo mortality is much higher than Norwegian mortality from lung cancer. In Table 23 expected numbers are given on both an Oslo and a Norwegian basis for the period 1941-57. The sexes are shown separately in this Table.

Actual deaths are about twice the number expected on an Oslo basis. The same relationship was found for cancers of the pharynx and larynx. The mortality ratio appears to be about the same for both ulcer sites and for both operated and unoperated. The two sexes show no gross difference, but the data for females are too scanty to allow any conclusions.

Unfortunately only fragmentary information has been collected on the smoking habits of these patients.

Autopsy results are available for 20 of the 23 deaths in Table 22. In the remaining 3 cases the diagnosis was confirmed histologically.

Table 22

## Cancer of lung

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status, site of ulcer, type of operation, and years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$
NOT OPERATED												
Gastric ulcer	1	1		4	2		11	5	5	1.6	8	5
Duodenal ulcer	1			.5	3	4	7	2	3	1.3	5	7
OPERATED												
Gastric ulcer												
Resection	0			.2			1	2	2	.3	2	2
Gastrojejunostomy	0		1	0			1			1		1
Both operations	1		1	.2			.2	2	2	.3	2	3
Duodenal ulcer												
Resection	1			4	3	3	.3	2	2	.8	5	5
Gastrojejunostomy	0			.2	1	2	.5	1	1	7	2	3
Both operations	1			.6	4	5	.8	3	3	1.6	7	8

Table 23

## Cancer of lung

Calendar years 1941-57

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by sex, operation status, and site of ulcer

	$E_N$	$E_O$	$D_O$	$D_R$
NOT OPERATED				
Gastric ulcer				
Males	.8	2.1	4	4
Females	4	2	1	1
M + F	1.3	2.7	5	5
Duodenal ulcer				
Males	.9	2.3	4	5
Females	.2	.3	1	1
M + F	1.1	2.6	5	6
OPERATED				
Gastric ulcer				
Males	4	10	2	2
Females	1	1		
M + F	.5	1.1	2	2
Duodenal ulcer				
Males	1.3	3.4	7	7
Females	1	1		
M + F	1.4	3.5	7	7

## LEUKAEMIA AND ALEUKAEMIA

Table 24 gives data for both the entire period 1917-57 and for 1941-57. For the latter period expected deaths are given on both a Norwegian and an Oslo basis.

Table 24

### Leukaemia and aleukaemia

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by site of ulcer, operation status, and calendar year period

For the years 1941-57 Deaths expected on basis of Oslo mortality ( $E_O$ )

	Calendar year period						
	1917-57			1941-57			
	$E_N$	$D_C$	$D_R$	$E_N$	$E_O$	$D_C$	$D_R$
<b>NOT OPERATED</b>							
Gastric ulcer	1.2	3	3	1.0	1.3	3	3
Duodenal ulcer	.9	5	5	.8	1.0	4	4
Both sites	2.2	8	8	1.7	2.3	7	7
<b>OPERATED</b>							
Gastric ulcer	.3	1	1	.3	.4		
Duodenal ulcer	1.0	2	1	.9	1.1	2	1
Both sites	1.3	3	2	1.2	1.5	2	1

The numbers are small. Nevertheless, the excess mortality for unoperated patients is noteworthy. Operated patients had normal mortality.

Autopsy was performed in 8 of the 10 deaths in Table 24. In the remaining 2 cases the diagnosis was based on bone marrow examination. The type of leukaemia was stated as

Paramyeloblastic	4
Acute aleukaemic	1
Myeloid	4
Lymphatic	1

The distribution is not markedly different from the one recorded by the Cancer Registry of Norway (10) for new cases in Norway in 1953-4.

No useful estimates can be made of the amount and time of exposure to radiation.

## ALL OTHER MALIGNANT TUMOURS

The data are shown in Table 25.

This cause group is one of the few where there is a noteworthy discrepancy between deaths according to the official and revised codes. This complicates the interpretation.

Gastric ulcer patients, both operated and unoperated, have very nearly normal mortality. For duodenal ulcer patients, however, there is an excess which is largely limited to 15 or more years after discharge or operation. In this subgroup the mortality ratio is about 2 for both operated and unoperated



Table 25

All other malignant tumours

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, site of ulcer type of operation, and years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	.9	1	2	2.2	1	4	4.8	7	8	7.9	9	14
Females	2.2	1	2	5.1	4	7	9.4	11	12	16.7	16	21
M + F	3.1	2	4	7.3	5	11	14.2	18	20	24.6	25	35
Duodenal ulcer												
Males	.9	1		2.5	2	1	3.3	9	11	6.7	12	12
Females	1.1	2	2	2.7	4	5	2.5	4	5	6.3	10	12
M + F	2.0	3	2	5.2	6	6	5.8	13	16	13.0	22	24
<b>OPERATED</b>												
Gastric ulcer												
Resection												
Males	.2			7			7			1.6		
Females	.3			7			11	2	2	1.6	2	2
M + F	.5			14			1.3	2	2	3.2	2	2
Gastrojejunostomy												
Males	1			.3			.6	1	2	1.0	1	2
Females	1			.2			4	1	1	.6	1	1
M + F	.2			.5			1.0	2	3	1.6	2	3
Both operations												
Males	.3			1.0			1.3	1	2	2.6	1	2
Females	4			.9			.9	3	3	2.2	3	3
M + F	7			1.8			2.2	4	5	4.8	4	5
Duodenal ulcer												
Resection												
Males	.6	1	2	1.7	2	3	1.2	2	1	3.5	5	11
Females	.3			7	3	3	.5	1	1	1.5	4	4
M + F	.9	1	2	2.3	5	6	1.8	3	2	5.0	9	10
Gastrojejunostomy												
Males	4			1.2	1	2	3.0	8	7	4.6	11	9
Females	.3			7			1.2	1	1	2.2	1	1
M + F	7			1.9	1	2	4.2	9	8	6.8	10	10
Both operations												
Males	1.0	1	2	2.9	3	5	4.2	10	8	8.1	14	15
Females	.5			1.4	3	3	1.8	2	2	3.7	5	5
M + F	1.5	1	2	4.2	6	8	6.0	12	10	11.7	19	20

duodenal ulcer patients. In Table 10 it was found that deaths expected on an Oslo basis exceeded deaths expected on a Norwegian basis by about 15 % in 1951-7. It seems unlikely that in previous years the difference between the two expectancies can have been so high as to explain the excess in Table 25.

The deaths according to the revised code in Table 25 can be specified as follows

	NOT OPERATED		OPERATED	
	Gastric ulcer	Duodenal ulcer	Gastric ulcer	Duodenal ulcer
Cancer of tongue	1	1		
Sarcoma of mediastinum	1			
Cancer of breast	12	2		3
Cancer of uterus	1	4	1	
Cancer of ovary	4	1		1
Cancer of prostate	6	5		3
Cancer of testis				2
Cancer of kidney		2		1
Cancer of urinary bladder	2	2		
Malignant melanoma	1	1		3
Gliomas	2		1	1
Sarcoma duræ				1
Malignant neurinoma			1	1
Cancer of thyroid gland	1			
Cancer of thymus	1			
Osteosarcoma		2	1	
Ewing sarcoma				1
Cancer of columna (metastatic?)	1			
Cancer of abdomen	1	2	1	2
Malignant lymphoma	1			
Multiple myeloma		2		1
	35	24	5	20

In this listing no single localization stands out as being responsible for the excess among duodenal ulcer patients. Malignant melanomas probably show the largest mortality ratio expected deaths among duodenal ulcer patients, based on the mortality rates in Oslo in 1951-7 were .9 from this cause, against 4 actual deaths.

In large prospective studies Hammond & Horn (11) and Dorn (12) found cancer of prostate and cancer of urinary bladder to be cigarette-associated. In the present material deaths in unoperated patients from these causes (11 prostate and 4 bladder cancers) number roughly twice the expected. In operated patients, however there are no bladder cancer deaths against roughly 1 expected, and the number of prostate cancers - 3 - is more or less equal to expectation.

Autopsy was performed in 41 of the 84 deaths according to the revised code in Table 25

#### DIABETES

Dotevall (13) estimated the incidence of duodenal ulcer in diabetics to be less than expected on the basis of the general population incidence. The incidence of gastric ulcers was about as expected.

Table 26 appears to show a corresponding relationship duodenal ulcer patients rarely get diabetes. However a low mortality is found for gastric ulcer patients as well.

Table 26

## Diabetes

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by site of ulcer and operation status

	$E_N$	$D_C$	$D_R$
NOT OPERATED			
Gastric ulcer	4.4	2	
Duodenal ulcer	2.2		
OPERATED			
Gastric ulcer	7		
Duodenal ulcer	1.9	1	1
NOT OPERATED and OPERATED			
Gastric ulcer	5.1	2	
Duodenal ulcer	4.0	1	1

For diabetics, as well as for patients with a number of the cardio-vascular respiratory conditions to be discussed later the assignment of a single revised cause of death is often quite arbitrary. Therefore, the comparison should be made primarily between deaths according to the official code and the expected number of deaths.

In only a fraction of the cases where diabetes is entered on the death certificate is this disease coded as the underlying cause. Comparison of actual and expected diabetes deaths is therefore an insensitive method for studying the association, if the comparison is based, as in Table 26 on the main or underlying cause of death. For many years, however the Central Bureau of Statistics has prepared separate Tables, by age and sex, of all death certificates with mention of diabetes. The Institute has used these statistics to compute, for the period 1941-57 expected percentages of death certificates with mention of diabetes in the material. It should be remembered that the statistics refer to Norway as a whole. There may be a difference between Oslo and Norway in the frequency with which diabetes is entered as a contributory cause, even if there is little difference between main cause rates. Actual and expected percentages for 1941-57 turn out as follows

	Number of deaths	Percentage with diabetes on certificate	
		Actual	Expected
Gastric ulcer			
Not operated	274	2.2	2.1
Operated	62	0	2.0
Total	336	1.8	2.1
Duodenal ulcer			
Not operated	175	0	1.8
Operated	193	2.6	1.8
Total	368	1.4	1.8

These differences could easily be due to chance. However the contrast between unoperated and operated duodenal ulcer patients may be noteworthy. It is known that hyperglycaemia reduces acid secretion. Conversely could the amount of gastric acid be of importance in diabetes pathogenesis?

In summary the present data on diabetes mortality are inconclusive.

### AIPOPLEXY

Table 27 shows the data by years from discharge for unoperated and by years from operation for operated patients.

Table 27

Apoplexy

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status, site of ulcer and years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer	5.1	9	11	13.0	21	22	26.0	26	30	44.1	56	63
Duodenal ulcer	3.1	4	3	8.7	5	7	10.6	12	11	22.4	21	21
<b>OPERATED</b>												
Gastric ulcer												
Resection	.6	3	2	2.1	2	2	2.3	3	3	5.0	8	7
Gastrojejunostomy	.3	1	1	.8	1	1	1.9	3	3	3.0	3	5
Both operations	.9	4	3	2.8	3	3	4.2	6	6	8.0	13	12
Duodenal ulcer												
Resection	.9			2.7			2.3	1	1	6.2	1	1
Gastrojejunostomy	1.1	2	1	3.4	2	3	8.9	3	5	13.4	7	9
Both operations	2.0	2	1	6.1	2	3	11.4	4	6	19.5	8	10

Unoperated gastric ulcer patients have a slight excess mortality. A similar excess is seen for operated gastric ulcer. For operated duodenal ulcer patients there is a marked deficit.

In Table 28 the data are distributed by age and sex.

The two sexes do not differ much. For age under 70 the pattern is more distinct than for all ages: an excess among gastric ulcer patients and a deficit among duodenal ulcer patients. The deviations from expected deaths are more pronounced for operated than for unoperated patients.

Comparison with Oslo mortality can be made only for the period 1951-7 as shown in Table 29.

Norwegian and Oslo mortality give nearly the same expected numbers of deaths from this cause. Table 29 has preserved the deficit for operated duodenal ulcer but there is little indication of the excess for gastric ulcer patients which was found in Tables 27 and 28.

Table 26

## Diabetes

Actual deaths according to official code ( $D_0$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by site of ulcer and operation status

	$E_N$	$D_0$	$D_R$
NOT OPERATED			
Gastric ulcer	4.4	2	
Duodenal ulcer	2.2		
OPERATED			
Gastric ulcer	7		
Duodenal ulcer	1.9	1	1
NOT OPERATED and OPERATED			
Gastric ulcer	5.1	2	
Duodenal ulcer	4.0	1	1

For diabetics, as well as for patients with a number of the cardio-vascular respiratory conditions to be discussed later the assignment of a single revised cause of death is often quite arbitrary. Therefore the comparison should be made primarily between deaths according to the official code and the expected number of deaths.

In only a fraction of the cases where diabetes is entered on the death certificate is this disease coded as the underlying cause. Comparison of actual and expected diabetes deaths is therefore an insensitive method for studying the association, if the comparison is based, as in Table 26 on the main or underlying cause of death. For many years, however the Central Bureau of Statistics has prepared separate Tables, by age and sex, of all death certificates with mention of diabetes. The Institute has used these statistics to compute, for the period 1941-57 expected percentages of death certificates with mention of diabetes in the material. It should be remembered that the statistics refer to Norway as a whole. There may be a difference between Oslo and Norway in the frequency with which diabetes is entered as a contributory cause, even if there is little difference between main cause rates. Actual and expected percentages for 1941-57 turn out as follows

	Number of deaths	Percentage with diabetes on certificate	
		Actual	Expected
Gastric ulcer			
Not operated	274	2.2	2.1
Operated	62	0	2.0
Total	336	1.8	2.1
Duodenal ulcer			
Not operated	175	0	1.8
Operated	193	2.6	1.8
Total	368	1.4	1.8

# CORONARY HEART DISEASE

Table 30 shows actual deaths in relation to deaths expected on a Norwegian basis for the entire period 1917-57

Table 30

## Coronary heart disease

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, site of ulcer type of operation, and years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	.9	2	3	3.0	2	3	11.3	20	18	13.2	24	24
Females	1.0			3.9	4	5	10.7	18	17	15.6	22	22
M + F	1.9	2	3	6.9	6	8	21.9	38	35	30.8	46	46
Duodenal ulcer												
Males	1.0	2	2	3.8	6	5	8.5	9	13	13.3	17	20
Females	.6		1	2.4	2	2	3.3	1	1	6.4	3	4
M + F	1.6	2	3	6.3	8	7	11.8	10	14	19.7	20	24
<b>OPERATED</b>												
Gastric ulcer												
Resection												
Males	.3			1.5	3	3	1.8	3	3	3.6	6	6
Females	.2			.7			.7	2	2	1.5	2	2
M + F	.5			2.1	3	3	2.5	5	5	5.1	8	8
Gastrojejunostomy												
Males	1			4	1	1	1.5	2	2	1.9	3	3
Females	.0			1			.4			.5		
M + F	1			4	1	1	1.9	2	2	2.5	3	3
Both operations												
Males	4			1.8	4	4	3.3	5	5	3.5	9	9
Females	.2			.7			1.1	2	2	2.1	2	2
M + F	.6			2.6	4	4	4.4	7	7	7.6	11	11
Duodenal ulcer												
Resection												
Males	.8	1	1	3.4	8	7	3.2	6	6	7.5	13	14
Females	1			.3			.6	1	1	.9	1	1
M + F	.9	1	1	3.7	8	7	3.7	7	7	8.3	16	15
Gastrojejunostomy												
Males	4			1.7	3	3	7.1	11	10	9.2	14	13
Females	1			.5	1	2	2.0	3	4	2.6	4	6
M + F	.5			2.2	4	5	9.1	14	14	11.8	18	19
Both operations												
Males	1.2	1	1	5.2	11	10	10.3	17	18	16.7	29	27
Females	.2			.8	1	2	2.5	4	5	3.5	5	7
M + F	1.4	1	1	5.9	12	12	12.8	21	23	20.2	34	34

Actual deaths exceed expectation for unoperated gastric ulcer patients and for operated patients of both ulcer sites. However the excess is not much greater than corresponding to the ratio of 1.4 between expectancies on an Oslo and a Norwegian basis in 1951-7 (Table 10). Unoperated duodenal ulcer patients show very nearly the number of deaths that would be expected on a Norwegian basis.

There is no evidence in Table 30 of any differences in mortality ratio between sexes, between operation types, or between the time periods after the start of observation.

Table 31 is limited to the period 1951-7. It gives expected deaths both on an Oslo basis and on a Norwegian basis, and shows separately the data for age under 60.

*Table 31*  
Coronary heart disease  
Calendar year period 1951-57  
Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by sex, age, operation status, and site of ulcer

	Age attained											
	Under 60				60 and over				All ages			
	$E_N$	$E_O$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	1.3	2.0	3	3	6.5	9.4	11	10	7.8	11.3	14	13
Females	4	4	2	2	6.9	8.2	8	5	7.2	8.6	10	7
M + F	1.7	2.4	5	5	13.3	17.5	19	15	15.0	19.9	24	20
Duodenal ulcer												
Males	2.0	3.0	2	3	5.8	8.4	5	7	7.8	11.3	7	10
Females	2	2			3.1	3.7	1		3.2	3.8	1	
M + F	2.1	3.1	2	3	8.9	12.0	6	7	11.0	15.2	8	10
<b>OPERATED</b>												
Gastric ulcer												
Males	.8	1.2	3	3	2.8	4.1	3	3	3.6	5.3	6	6
Females	1	1			1.2	1.5	2	2	1.3	1.5	2	2
M + F	.9	1.3	3	3	4.1	5.6	5	5	4.9	6.9	8	8
Duodenal ulcer												
Males	3.5	5.4	10	9	7.2	10.5	10	9	10.7	15.8	20	18
Females	1	1			1.8	2.1	4	4	1.9	2.2	4	4
M + F	3.6	5.5	10	9	9.0	12.6	14	13	12.6	18.1	24	22

The differences between actual deaths and deaths expected on an Oslo basis are no greater than might be ascribed to chance. However it is noteworthy that whereas unoperated duodenal ulcer patients show a deficit in actual deaths, there is an excess for operated patients. In view of the different time trends over the past decades of apoplexy and coronary heart disease it may be of interest to summarize the findings for the two conditions in duodenal ulcer patients in 1951-7.

	Duodenal ulcer 1931-57		Duodenal ulcer 1931-57	
	Not operated E <sub>O</sub>	D <sub>O</sub>	Operated E <sub>O</sub>	D <sub>C</sub>
Apoplexy				
All ages	9.1	8	9.1	3
Coronary heart dis.				
Age under 60	3.1	2	5.5	10
All ages	15.2	8	18.1	24

The basis for cause of death for the 115 patients in Table 30 (revised code) can be summarized as follows

	NOT OPERATED		OPERATED		TOTAL
	Gastric	Duodenal	Gastric	Duodenal	
Autopsy	15	9	5	14	43
No autopsy died in hospital	5	3		1	■
No autopsy died outside hospital					
Coronary h.d. diagnosed in hospital prior to death	5	4	1	4	14
Others	21	8	5	15	49
	46	24	11	34	115

#### SUDDEN DEATH - HEART PARALYSIS

Data are given in Table 32

Table 32

##### Sudden death - heart paralysis

Actual deaths according to official code (D<sub>C</sub>) and according to revised code (D<sub>R</sub>) and deaths expected on basis of Norwegian mortality (E<sub>N</sub>) by sex, operation status, site of ulcer and calendar year period

For the period 1931-57 Deaths expected on basis of Oslo mortality (E<sub>O</sub>)

	Calendar year period						
	1917-57			1931-57			
	E <sub>N</sub>	D <sub>O</sub>	D <sub>R</sub>	E <sub>N</sub>	E <sub>O</sub>	D <sub>O</sub>	D <sub>R</sub>
<b>NOT OPERATED</b>							
Gastric ulcer							
Males	4.6	10	11	7	7	2	2
Females	3.4	5	3	4	4		
M + F	8.0	15	14	11	11	2	2
Duodenal ulcer							
Males	3.4	6	4	.8	.8	1	
Females	.9	2	2	.2	.2	1	1
M + F	4.4	8	6	1.0	1.0	2	1
<b>OPERATED</b>							
Gastric ulcer							
Males	1.3	2	2	4	4		
Females	.3			1	1		
M + F	1.6	2	2	4	4		
Duodenal ulcer							
Males	4.1	7	6	1.2	1.2	3	3
Females	.6	2		1	1		
M + F	4.7	9	6	1.3	1.3	3	3



There is a suggestion of excess mortality from this cause both in gastric and duodenal ulcer patients.

Some of the deaths were probably due to coronary heart disease. It may be noted that Table 32 gives no support to the possible assumption that the slight coronary heart disease excess in operated duodenal ulcer patients in Table 31 might be due to a diagnostic transfer from sudden death.

All the 28 deaths (revised code) in Table 32 took place outside hospital. There was no autopsy.

### VALVULAR HEART DISEASE

Data are given in Tables 33 and 34. The latter refers only to the years 1951-7 and gives expected deaths on both a Norwegian and an Oslo basis.

Table 33

#### Valvular heart disease

Actual deaths according to official code ( $D_0$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, site of ulcer and years from discharge/operation.

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$	$E_N$	$D_0$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	1.4	4	1	2.4	2	1	2.5	4	1	6.5	10	3
Females	2.1	1		4.0	10	2	4.0	5	5	10.1	16	7
M + F	3.5	5	1	6.4	12	3	6.5	9	6	16.5	26	10
Duodenal ulcer												
Males	1.3	2		1.9	5	4	1.2	2	2	4.4	9	6
Females	.8	2		1.5	1	2	.8			3.0	3	2
M + F	2.0	4		3.4	6	6	2.0	2	2	7.3	12	8
<b>OPERATED</b>												
Gastric ulcer												
Males	.3	1	1	7	2	1	.6			1.6	3	2
Females	.2			4			.3			.9		
M + F	.6	1	1	11	2	1	9			2.5	3	2
Duodenal ulcer												
Males	1.1	1	1	2.1	5	5	1.9	1	2	5.0	7	8
Females	.3			.8	1		.8	1		1.9	2	
M + F	1.4	1	1	2.9	6	5	2.6	2	2	6.9	9	8

For this cause the number of deaths according to the revised code is much smaller than according to the official code. This is mainly due to the fact that in official statistics prior to 1951 the diagnosis *Vitium org cordis* has been included in the groups defined as Valvular heart disease in Appendix II. In the revised code this diagnosis has been transferred to Other diseases of cardiovascular system.

*Table 31*  
Valvular heart disease  
Calendar year period 1951-57

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by operation status and site of ulcer

	$E_N$	$E_O$	$D_C$	$D_R$
NOT OPERATED				
Gastric ulcer	1.7	1.8	3	4
Duodenal ulcer	1.1	1.2	1	2
OPERATED				
Gastric ulcer	.5	.5		
Duodenal ulcer	1.2	1.3		

In Table 33 expected deaths mostly fall between the two categories of actual deaths.

In 7 of the 28 cases according to the revised code in Table 33 the heart disease was specified as a discharge diagnosis in addition to the ulcer at the start of observation.

Autopsy had been performed in 19 of the 28 deaths. Five other patients died in hospital but without autopsy.

#### OTHER DISEASES OF CARDIO-VASCULAR SYSTEM

Data are given in Tables 35 and 36. The latter refers only to the years 1951-7 and gives expected deaths on both a Norwegian and an Oslo basis.

*Table 35*  
Other diseases of cardio-vascular system

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, site of ulcer and years from discharge/operation

Number of years from discharge/operation												
0-4			5-14			15 +			All years			
$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$	$E_N$	$D_C$	$D_R$	
NOT OPERATED												
Gastric ulcer												
Males	1.4	3	3	2.8	4	3	6.7	4	6	10.9	11	12
Females	1.6		2	3.1	2	11	10.2	7	7	16.8	9	20
M + F	2.9	3	5	7.9	6	11	16.9	11	11	27.7	20	32
Duodenal ulcer												
Males	1.2	1	2	2.7	1	1	4.1	2	1	8.1	4	4
Females	.8			2.6	4	4	2.9			6.3	4	4
M + F	2.0	1	2	3.3	5	5	7.0	2	1	14.4	8	11
OPERATED												
Gastric ulcer												
Males	.3			1.1			1.8	1	2	3.2	1	2
Females	.2			.7	1	1	.9	1	1	1.8	2	2
M + F	.5			1.8	1	1	2.7	2	3	5.0	3	4
Duodenal ulcer												
Males	1.0	1	2	3.1	4	3	5.1	8	7	9.2	11	12
Females	.2			.8		1	2.4	1	2	3.3	1	3
M + F	1.2	1	2	3.8	4	4	7.4	9	9	12.5	14	15

Table 35

Other diseases of cardio-vascular system

Calendar year period 1951-57

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by operation status and site of ulcer

	$E_N$	$E_O$	$D_O$	$D_R$
NOT OPERATED				
Gastric ulcer	9.5	9.1	6	4
Duodenal ulcer	6.1	6.0	3	1
OPERATED				
Gastric ulcer	2.6	2.6	1	2
Duodenal ulcer	5.9	6.1	8	6

The large discrepancy between deaths according to the official code and deaths according to the revised code is accounted for by the deaths transferred from 'Valvular heart disease' during the revision.

There are no large differences between actual and expected deaths in Table 35 or Table 36.

The basis for cause of death is much poorer than in the group 'Valvular heart disease' autopsy was performed in 12 of the 59 deaths (revised code) in Table 35. Another 17 patients died in hospital without autopsy while the remaining 30 died outside hospital.

In view of the difficulty of making a useful distinction between this cause group and the preceding one it may be as well to pool them.

	Valvular heart disease + Other diseases of cardio-vascular system		
	$E_N$	$D_O$	$D_R$
NOT OPERATED			
Gastric	44.0	46	42
Duodenal	21.8	20	16
OPERATED			
Gastric	7.5	6	6
Duodenal	19.4	23	23

There is no evidence of any abnormal mortality in this combined group.

#### PNEUMONIA

Data for the entire period 1917-57 with expected deaths based on Norwegian mortality are presented in Table 37.

Actual deaths are clearly in excess of expected deaths. However in Table 10 it was shown that for 1951-7 the expectancy on an Oslo basis was about 45 % higher than on a Norwegian basis. Table 38 gives data for the period 1941-57 with expected deaths according to both bases, and with a break-down by age.

Table 37

## Pneumonia

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, site of ulcer and years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$	$E_N$	$D_O$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	2.2	4	4	3.2	6	7	4.4	12	11	9.7	22	22
Females	2.5	3	5	5.6	10	9	7.1	7	5	15.1	20	19
M + F	4.7	7	9	8.8	16	16	11.4	19	16	24.9	42	41
Duodenal ulcer												
Males	1.9	2	1	2.9	6	6	2.1	4	4	7.0	12	11
Females	1.1	1	1	2.5	2		1.6	3	3	5.1	6	4
M + F	3.0	3	2	5.4	8	6	3.7	7	7	12.1	18	15
<b>OPERATED</b>												
Gastric ulcer												
Males	.5	1	1	.9	2	2	1.1	3	2	2.4	6	5
Females	.2	2	2	.5	1	1	.5			1.3	3	3
M + F	.7	3	3	1.5	3	3	1.5	3	2	3.7	9	8
Duodenal ulcer												
Males	1.6			2.9	12	8	3.0	6	4	7.5	16	12
Females	.3	2	2	.9			1.5	2	3	2.7	4	5
M + F	1.9	2	2	3.7	12	8	4.5	8	7	10.1	22	17

It should be noted that the difference between the two types of expected deaths is larger than indicated by Table 10 because in 1941-50 the difference between Oslo and Norwegian pneumonia death rates was greater than in 1951-7. Different coding practices may have played a part during 1941-50.

The actual deaths in Table 38 come close to the number expected on the basis of Oslo mortality. There is a suggestion of excess in operated patients under 60.

It is of interest to compare Table 38 with the corresponding Table 12 for tuberculosis of the respiratory system. The excess in unoperated gastric ulcer patients of tuberculosis deaths is not matched by pneumonia deaths. Further operated patients at age 50 and above had an increased tuberculosis mortality whereas there is no excess of pneumonia deaths in operated patients age 60 and above.

Autopsy was performed in 33 of the 81 deaths in Table 37 (revised code). Another 19 patients died in hospital without autopsy while the remaining 29 died outside hospital.

Table 38

## Pneumonia

Calendar year period 1941-57

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by sex, age, operation status, and site of ulcer

	Age attained											
	Under 60				60 and over				All ages			
	$E_N$	$E_O$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	.9	1.6	3	4	3.7	7.9	12	12	4.6	9.5	15	16
Females	.6	.7			7.7	13.5	9	7	8.5	14.2	9	7
M + F	1.5	2.3	3	4	11.5	21.4	1	19	12.9	23.8	24	23
Duodenal ulcer												
Males	1.2	2.1	2	2	5.0	6.5	3	3	4.2	8.5	5	5
Females	.3	.3	1		3.6	6.3	5	4	3.8	6.6	6	4
M + F	1.5	2.4	3	2	6.6	12.7	8	7	8.1	15.1	11	9
<b>OPERATED</b>												
Gastric ulcer												
Males	4	7	3	3	11	2.2			1.5	2.9	3	3
Females	1	1			.9	1.4	1	1	1.0	1.5	1	1
M + F	.3	.8	3	3	1.9	3.6	1	1	2.4	4.4	4	4
Duodenal ulcer												
Males	1.5	2.6	4	2	3.1	6.4	7	4	4.5	9.0	11	6
Females	1	.2			1.6	2.7	2	3	1.8	2.9	2	3
M + F	1.6	2.8	4	2	4.7	9.1	9	7	6.3	11.9	13	9

## BRONCHITIS AND ASTHMA

Table 39 shows that there is no evidence of any abnormal mortality

Table 39

## Bronchitis and asthma

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status and site of ulcer

	$E_N$	$D_O$	$D_R$
<b>NOT OPERATED</b>			
Gastric ulcer	5.3	4	3
Duodenal ulcer	2.4	1	2
<b>OPERATED</b>			
Gastric ulcer	.8	1	1
Duodenal ulcer	2.5	3	3

Autopsy was performed in 3 of the 9 deaths (revised code) in Table 39. The 6 other patients died outside hospital.

The term *Asthma bronchiale* was used on 4 of the 9 certificates.

## OTHER DISEASES OF RESPIRATORY ORGANS

In this cause group the comparison between deaths according to the official code and expected deaths will be biased. Several postoperative deaths in this material have been certified as due to a pulmonary embolus rather than the condition which caused the operation — peptic ulcer in most cases. Such deaths have been counted in official statistics in Other diseases of respiratory organs as defined in Appendix II. But peptic ulcer patients, particularly if unoperated, have a much higher risk than the general population of being operated upon. Table 40 must therefore be interpreted as showing no excess mortality from this cause group.

Table 40

Other diseases of respiratory organs  
Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status and site of ulcer

	$E_N$	$D_C$	$D_R$
NOT OPERATED			
Gastric ulcer	2.4	7	3
Duodenal ulcer	1.5	3	3
OPERATED			
Gastric ulcer	.5		
Duodenal ulcer	1.6	1	1

Autopsy was performed in 6 of the 7 deaths in Table 40. The remaining death took place in hospital, but without autopsy.

## GASTRO-DUODENAL ULCER

It is important to remember that postoperative deaths, i.e. deaths in the course of the hospital stay during which the first operation for peptic ulcer was performed, have been included in the unoperated group. Table 41 presents the data.

As might be expected, the excess mortality is greater during the first years after discharge or operation than in later years. However even after 15 or more years the mortality is greater than the general Norwegian mortality. There is no great difference between the mortality ratios for the two ulcer sites, or for the two sexes, or for the two operation types.

The type of complication which caused death can be summarized as follows

	NOT OPERATED		Total
	Gastric	Duodenal	
Postoperative (with or without haemorrhage or perforation) after			
Resection	11	17	28
Gastrojejunostomy	4	4	8
Unknown operation type	2		2
Haemorrhage	19	5	24
Perforation	7	6	13
Other and unspecified —	4	4	8
	47	36	83

	Resection	OPERATED G.J.stomy	Total
Postoperative after resection		2	2
Gastrojejunal ulcer	3	8	11
Perforation in stomach-duodenum	3	1	4
Haemorrhage	3	2	5
Other and unspecified	5	4	9
	14	17	31

Table 41

Gastro-duodenal ulcer

Actual deaths according to official code (D<sub>G</sub>) and according to revised code (D<sub>R</sub>) and deaths expected on basis of Norwegian mortality (E<sub>N</sub>) by sex, operation status, site of ulcer type of operation, and number of years from discharge/operation

	Number of years from discharge/operation											
	0-4			5-14			15 +			All years		
	E <sub>N</sub>	D <sub>G</sub>	D <sub>R</sub>	E <sub>N</sub>	D <sub>G</sub>	D <sub>R</sub>	E <sub>N</sub>	D <sub>G</sub>	D <sub>R</sub>	E <sub>N</sub>	D <sub>G</sub>	D <sub>R</sub>
<b>NOT OPERATED</b>												
Gastric ulcer												
Males	4	17	19	7	13	13	7	11	2	1.8	32	34
Females	.2	11	7	4	3	2	4	4	4	1.0	18	13
M + F	.6	28	26	11	16	15	1.2	6	6	2.8	50	47
Duodenal ulcer												
Males	.5	15	17	7	6	9	4	3	4	1.6	24	30
Females	1	3	4	.2	2	2	1			.3	5	6
M + F	.5	18	21	.9	8	11	.5	3	4	1.9	29	36
<b>OPERATED</b>												
Gastric ulcer												
Resection												
Males	1	2	2	1			1			.5	2	2
Females	.0	1	1	.0	1	1	.0			1	2	2
M + F	1	3	3	.2	1	1	1			4	4	4
Gastrojejunostomy												
Males	.0			1	1	2	1			.2	1	2
Females	.0			.0			0	1	1	.0	1	1
M + F	.0			1	1	2	1	1	1	.2	2	3
Both operations												
Males	1	2	2	.2	1	2	.2			.5	3	4
Females	.0	1	1	0	1	1	.0	1	1	1	3	3
M + F	1	3	3	.3	2	3	.2	1	1	.6	6	7
Duodenal ulcer												
Resection												
Males	.2	4	4	4	2	5	.2			.8	8	9
Females	.0			0	1	1	.0			1	1	1
M + F	.3	4	4	4	3	6	.2			.9	7	10
Gastrojejunostomy												
Males	.2	4	4	4	3	8	.5	2	2	1.0	9	14
Females	0			.0			1			1		
M + F	.2	4	4	4	3	8	.5	2	2	1.2	9	14
Both operations												
Males	4	11	8	.8	5	13	.6	2	11	1.9	15	23
Females	.0			1	1	1	1			.2	1	1
M + F	.5	8	8	.9	6	14	7	2	2	2.1	16	24

Autopsy was performed in 64 of the 114 deaths in Table 41. Another 34 patients died in hospital without autopsy while the remaining 16 died outside hospital.

#### ILEUS AND HERNIA

As can be seen from Table 42 there are few deaths from this cause. There is at most a small increase in risk for operated patients.

Table 42

##### Ileus and hernia

Actual deaths according to official code ( $D_0$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status and site of ulcer

	$E_N$	$D_0$	$D_R$
NOT OPERATED			
Gastric ulcer	3.5	2	3
Duodenal ulcer	1.8	4	4
Both sites	5.3	6	7
OPERATED			
Gastric ulcer	.6	1	1
Duodenal ulcer	1.6	4	5
Both sites	2.2	5	6

Autopsy was performed in 10 of the 13 deaths in Table 42. The remaining 3 patients died in hospital without autopsy.

The cause of obstruction was

	Not operated	Operated
Invagination into operated stomach		1
Adhesions, with kinking or strangulation of small intestine	2	3
Invagination of the ileum		1
Volvulus of sigmoid colon	1	
Incarcerated inguinal hernia	1	
Other and unspecified	3	1
	7	6

#### APPENDICITIS

Table 43 shows that there is no evidence of any abnormal mortality from this cause. There was autopsy in one case only.

Table 43

##### Appendicitis

Actual deaths according to official code ( $D_0$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status and site of ulcer

	$E_N$	$D_0$	$D_R$
NOT OPERATED			
Gastric ulcer	1.3	2	1
Duodenal ulcer	.9	3	2
OPERATED			
Gastric ulcer	.2		
Duodenal ulcer	.8	1	1



# CIRRHOSIS OF LIVER

Data from the present study are given in Table 44 (all observation years) and in Table 45 (years 1941-57)

Table 44

## Cirrhosis of liver

Actual deaths according to official code ( $D_G$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, site of ulcer and years from discharge/operation

		Number of years from discharge/operation											
		0-4			5-14			15 +			All years		
		$E_N$	$D_G$	$D_R$	$E_N$	$D_G$	$D_R$	$E_N$	$D_G$	$D_R$	$E_N$	$D_G$	$D_R$
<b>NOT OPERATED</b>													
Gastric ulcer													
Males		1	2	3	2		1	.3	1	1	.6	3	5
Females		0	1	2	1			.3	3	3	.5	4	5
M + F		1	3	5	3		1	.6	4	4	1.0	7	10
Duodenal ulcer													
Males		1		1	2	2	2	.2	1	1	.5	3	4
Females		.0			1			1	1	1	.2	1	1
M + F		1		1	3	2	2	.3	2	2	.7	4	5
<b>OPERATED</b>													
Gastric ulcer													
Males		0			1			1			.2		
Females		.0			0	1	1	.0			1	1	1
M + F		.0			1	1	1	1			.2	1	1
Duodenal ulcer													
Males		1			.2	1		.3			.6	1	
Females		.0			.0	1	1	1			1	1	1
M + F		1			.3	2	1	4			7	2	1

The differences between Norwegian and Oslo rates are large for this cause. However Table 45 shows that there is an excess mortality among unoperated patients, even if comparison is made with Oslo rates. The question is whether the ulcer diagnosis was correct for those patients who later died from cirrhosis of the liver. In 6 of the unoperated patients in Table 44 it is likely that the ulcer diagnosis was based on an haematemesis which in the light of subsequent autopsy can more reasonably be ascribed to bursting oesophageal varices. This does not apply to any of the 9 deaths of unoperated patients in Table 45. However only in 8 of the 9 cases is the ulcer diagnosis well established.

For operated patients where the ulcer diagnosis is reliable, Table 45 shows that actual deaths in 1941-57 were as expected on an Oslo basis.

Autopsy was performed in 14 of the 17 deaths in Table 44. One patient died in hospital without autopsy while two patients died at home.

Table 45

Cirrhosis of liver  
Calendar year period 1941-57

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) and on basis of Oslo mortality ( $E_O$ ) by sex, operation status, and site of ulcer

	$E_N$	$E_O$	$D_O$	$D_R$
NOT OPERATED				
Gastric ulcer				
Males	.3	.9	1	1
Females	.4	.9	3	3
M + F	7	1.8	4	4
Duodenal ulcer				
Males	.3	.9	3	4
Females	.2	.4	1	1
M + F	.5	1.3	4	5
OPERATED				
Gastric ulcer				
Males	1	4		
Females	1	.3	1	1
M + F	.2	.5	1	1
Duodenal ulcer				
Males	.5	1.3		
Females	1	.3	1	1
M + F	.6	1.5	1	1

#### DISEASES OF BILE DUCTS AND GALL BLADDER

Table 46 gives data for all observation years and also for the years 1951-7 separately

Expected deaths are so few that mortality becomes an insensitive index for this diagnostic group. Even so there is a noteworthy excess of deaths in operated patients. In 2 of the 3 deaths (revised code) in unoperated patients it is possible that the symptoms which led to the ulcer diagnosis may in fact have been caused by gall stones.

There was no autopsy of patients assigned to this cause in the revised code. Three died in hospital, four outside

#### NEPHRITIS

Data are presented in Table 47

There is a suggestion of excess mortality for duodenal ulcer patients, both operated and unoperated. However deaths according to the revised code are much fewer than according to the official code. Also, the mortality in 1951-7 was close to expectation.

Autopsy was performed in 5 of the 18 deaths according to the revised code in Table 47. Another 8 patients died in hospital, while 5 patients died at home.

Table 46

## Diseases of bile ducts and gall bladder

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, site of ulcer and calendar year period

For the period 1951-57 Deaths expected on basis of Oslo mortality ( $E_O$ )

	Calendar year period						
	1917-57			1951-57			
	$E_N$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$
<b>NOT OPERATED</b>							
Gastric ulcer							
Males	.5	1		1	.2		
Females	1.4	3	2	4	4		
M + F	1.9	4	2	.5	7		
Duodenal ulcer							
Males	4	1	1	1	.2		
Females	.5	1		.2	.2		
M + F	.9	2	1	.3	4		
<b>OPERATED</b>							
Gastric ulcer							
Males	1			1	1		
Females	.2	1	1	1	1	1	1
M + F	.3	1	1	1	.2	1	1
Duodenal ulcer							
Males	4	2	1	.2	.3	1	1
Females	.3	2	2	1	1		
M + F	7	4	3	.3	4	1	1

Table 47

## Nephritis

Actual deaths according to official code ( $D_O$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status, site of ulcer and calendar year period

For the period 1951-57 Deaths expected on basis of Oslo mortality ( $E_O$ )

	Calendar year period						
	1917-57			1951-57			
	$E_N$	$D_O$	$D_R$	$E_N$	$E_O$	$D_O$	$D_R$
<b>NOT OPERATED</b>							
Gastric ulcer	8.6	8	5	.9	.8	1	
Duodenal ulcer	4.6	9	5	7	.6	1	1
<b>OPERATED</b>							
Gastric ulcer	1.5	2	2	.3	.3		
Duodenal ulcer	4.6	10	6	.9	.8	1	1

# OTHER DISEASES OF URINARY AND GENITAL ORGANS

Data are presented in Table 48.

Table 48

Other diseases of urinary and genital organs

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, etc. of ulcer and calendar year period.

For the period 1951-57 Deaths expected on basis of Oslo mortality ( $E_O$ )

	Calendar year period						
	1917-57			1951-57			
	$E_N$	$D_C$	$D_R$	$E_N$	$E_O$	$D_C$	$D_R$
<b>NOT OPERATED</b>							
Gastric ulcer							
Males	4.7	7	7	1.1	1.0		1
Females	1.7	5	3	.3	.4	1	
M + F	6.4	12	10	1.4	1.4	1	1
Duodenal ulcer							
Males	3.3	3	3	1.1	1.0	1	1
Females	.6		1	.2	.2		1
M + F	3.9	3	4	1.2	1.2	1	2
<b>OPERATED</b>							
Gastric ulcer							
Males	1.2		1	.5	.5		
Females	.2			1	1		
M + F	1.4		1	.6	.5		
Duodenal ulcer							
Males	3.5	1	3	1.2	1.1		1
Females	.3	2	2	1	1	1	1
M + F	3.8	3	5	1.3	1.2	1	

There is no evidence of any abnormal mortality. The suggestion of excess for unoperated gastric ulcer patients for 1917-57 as a whole is not sustained in 1951-7.

The causes of death can be specified as follows:

	NOT OPERATED		OPERATED	
	Gastric	Duodenal	Gastric	Duodenal
Adenoma of prostate	4	4	1	
Cystopneumothorax	2	2		4
Nephrolithiasis	1			
Other	3			1
	10	6	1	5

Autopsy was performed in 11 cases. Eight patients died in hospital without autopsy while the remaining 3 of the 22 deaths according to the revised code in Table 48 took place outside hospital.

## SENILITY

This cause has been included as an index of the level of certification of causes of death. A high proportion of deaths certified to senility or similarly ill-defined causes is often considered to be a sign of low quality mortality statistics. Table 49 gives the data.

Table 49

Senility  
Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by operation status, site of ulcer and calendar year period  
For the period 1941-57 Deaths expected on basis of Oslo mortality ( $E_O$ )

	Calendar year period						
	1917-57			1941-57			
	$E_N$	$D_C$	$D_R$	$E_N$	$E_O$	$D_C$	$D_R$
<b>NOT OPERATED</b>							
Gastric ulcer	23.9	11	11	12.3	4.6	3	3
Duodenal ulcer	8.1	7	7	6.6	2.4	5	5
Both sites	32.1	18	18	18.9	7.0	8	8
<b>OPERATED</b>							
Gastric ulcer	2.2			1.5	.5		
Duodenal ulcer	5.7	1	1	4.1	1.5		
Both sites	7.9	1	1	5.5	1.9		

Actual deaths are considerably below expectation on a Norwegian basis. There is a suggestion that the deficit may be larger for operated than for unoperated patients. During 1941-57 actual deaths came fairly close to the Oslo expectation.

The Table supports the idea that Oslo mortality is the better basis for comparison in this material.

There was no autopsy in the 19 deaths in Table 49. Ten patients died in hospital.

## SUICIDE

Data are presented in Table 50. For the period 1941-57 expected numbers of deaths are also given on an Oslo basis.

There is a distinct excess mortality. The mortality ratio in 1941-57 was slightly larger for unoperated than for operated and also slightly larger for duodenal than for gastric ulcer.

No useful information is available about alcohol consumption in the material. It may be noted, however, that Table 45 showed an excess of cirrhosis of liver in unoperated, but not in operated patients. For the period 1941-57 suicide and cirrhosis of liver can be compared as follows:

	Cirrhosis of liver				Suicide	
	$E_O$	$D_C$	$D_R$		$D_C$	$D_R$
Not operated	3.1	8	9	3.9	10	10
Operated	2.0	2	2	3.5	7	9

Table 50

## Suicide

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ), by sex, operation status, site of ulcer and calendar year period

For the period 1941-57: Deaths expected on basis of Oslo mortality ( $E_O$ )

	Calendar year period						
	1917-57			1941-57			
	$E_N$	$D_C$	$D_R$	$E_N$	$E_O$	$D_C$	$D_R$
<b>NOT OPERATED</b>							
Gastric ulcer							
Males	2.1	4	5	1.0	1.4	3	3
Females	.6	1	1	.5	.5	1	1
M + F	2.7	5	6	1.5	1.8	4	4
Duodenal ulcer							
Males	2.1	8	8	1.5	1.8	6	6
Females	.2	1	1	.2	.2		
M + F	2.4	9	9	1.5	2.1	6	6
<b>OPERATED</b>							
Gastric ulcer							
Males	7	2	3	.5	1	1	2
Females	1			.0	1		
M + F	7	2	3	.5	7	1	2
Duodenal ulcer							
Males	2.5	8	9	1.7	2.5	6	7
Females	1		1	1	1		
M + F	2.6	8	10	1.8	2.6	6	7

The numbers are small, but there is a hint that the suicide excess, at least in operated patients may not be associated with alcoholism.

The group Chronic alcoholism (See Table 8) does not have enough expected deaths to shed much light on the problem of frequency and effect of alcoholism in the material.

## ACCIDENTS AND HOMICIDE

Data are shown in Table 51

Operated duodenal ulcer patients show an excess for the period 1941-57. Otherwise, actual deaths come close to expected deaths. The cause of death can be specified as follows

	NOT OPERATED		OPERATED	
	Gastric	Duodenal	Gastric	Duodenal
Deaths in (or on way to) concentration camps	1	2		3
Other war deaths	1	4		2
Accidental drownings	3	1	1	2
Traffic accidents	5	1	1	1
Accidental burns		1		4
Accidental falls	6	4	1	4
Accidental intoxications	4			1
Other	1	1		3
	21	14	3	22

Table 51

## Accidents and homicide

Actual deaths according to official code ( $D_C$ ) and according to revised code ( $D_R$ ) and deaths expected on basis of Norwegian mortality ( $E_N$ ) by sex, operation status, site of ulcer and calendar year period

For the period 1941-57 Deaths expected on basis of Oslo mortality ( $E_O$ )

	Calendar year period						
	1917-57			1941-57			
	$E_N$	$D_C$	$D_R$	$E_N$	$E_O$	$D_C$	$D_R$
<b>NOT OPERATED</b>							
Gastric ulcer							
Males	11.3	15	15	6.4	5.7	5	10
Females	4.5	4	6	3.4	4.2	3	4
M + F	15.8	19	21	9.8	10.0	12	14
Duodenal ulcer							
Males	14.0	11	13	9.6	7.6	10	11
Females	1.9	1	1	1.7	2.0	1	1
M + F	15.9	12	14	11.2	9.7	11	12
<b>OPERATED</b>							
Gastric ulcer							
Males	3.7	4	3	2.6	2.4	2	1
Females	.5			.4	.5		
M + F	4.1	4	3	3.1	2.9	2	1
Duodenal ulcer							
Males	14.3	18	19	10.3	8.7	15	16
Females	.9	3	3	.8	.9	3	3
M + F	15.3	21	22	11.1	9.6	18	19

## OTHER CAUSES

## a) Multiple sclerosis

Mortality data for Norway and Oslo are only available for 1951-7 for this condition. If we apply the age sex-specific mortality rates for 1951-7 to the observation years in the total material, we get 2.1 expected deaths with Norwegian rates and 2.0 with Oslo rates. The material contained only one death where multiple sclerosis was mentioned on the certificate: male gastric ulcer not operated, died 12 years after discharge. The diagnosis of multiple sclerosis was verified at autopsy.

Accordingly there is no indication of any abnormal mortality from this cause.

## b) Amyotrophic lateral sclerosis

As in the case of multiple sclerosis, population death rates are available only for the period 1951-7. If we apply the Norwegian age-sex-specific rates for 1951-7 to the observation years for all calendar year periods, we get expected deaths as follows:

	Gastric ulcer	Duodenal ulcer	Both sites
NOT OPERATED	.5	.3	.8
OPERATED	1	.3	.3

Use of Oslo rates for 1951-7 gives practically the same expectations.

There were 5 deaths (1 male and 4 females) with this disease mentioned on the certificate. All were unoperated gastric ulcer patients. In 1 case another cause (Gastroenteritis) had been coded as the main cause of death. The diagnosis had been made in hospital for all 5 patients, but was verified by autopsy in only 1 case. In another case autopsy was performed, but the result of the microscopic examination of the nervous system was not found. The intervals between ulcer discharge and death were 3 11 14 24 and 31 years.

Ask Upmark (14) has suggested that gastric resection might increase the risk of contracting amyotrophic lateral sclerosis. There is no sign of this in the present material.

#### c) Pernicious anaemia

This diagnosis was found on 2 death certificates, in both cases as the main cause of death. Both patients were males, operated for gastric ulcer. One had a gastrojejunostomy 29 years prior to death. The other had a resection 12 years prior to death.

Expected deaths in the total material based on Norwegian death rates for 1951-7 were 6 for unoperated and .3 for operated patients.



## 4. Summary

The material consists of 3 662 patients who were discharged from the Ullevål Hospital during the years 1917-39 with a diagnosis of gastric or duodenal ulcer. Patients who had had a stomach operation prior to admission were excluded, as well as patients who died during their first stay.

An attempt was made to trace these patients to death, or to anniversary of discharge in 1957. About 3 / were lost sight of. 1,370 deaths at age 20 or over were recorded. As far as possible, the original death certificates were studied and the original cause-of-death code utilized in the classification of the deaths according to the definitions of Appendix II. The deaths were also classified on the basis of all available information, including autopsy results for about 40 / . The outcome of the alternative classifications has been shown throughout the report.

632 patients had an operation for their ulcer during first stay (Suturation of a perforated ulcer etc. has not been counted as an operation in this report). The rest were followed up with respect to later operations which were recorded for 969 patients.

The observation years, at age 20 and over in unoperated state numbered 47,268.0 and in operated state 27,094.0. These observation years were distributed by sex, age, calendar year period, site of ulcer, type of operation, and number of years after discharge (for unoperated state) or after operation. The number of years in each subgroup was multiplied by corresponding population death rates (Norwegian, to some extent also Oslo rate) to give expected number of deaths from the various causes. In the Tables of the report the subgroups have been pooled in different ways for the different causes of death.

The mortality ratio (actual to expected deaths) from all causes can be summarized as follows:

	Basis for expected deaths	
	Norway	Oslo
NOT OPERATED		
Males	1.67	1.36
Females	1.19	1.17
OPERATED		
Males	1.55	1.23
Females	1.15	1.12

Gastric ulcer patients had a higher mortality ratio than duodenal ulcer patients in unoperated state. After operation there was not much difference between the ulcer sites.

For unoperated patients the mortality ratio was higher during the first 5 years after discharge than in later years.

The main findings for the different causes of death were  
Pulmonary tuberculosis Excess mortality for unoperated gastric ulcer patients age 50 and above and for operated patients.

Cancer of oesophagus No abnormal mortality

Cancer of stomach Gross excess in first 5 years for unoperated gastric ulcer patients. Subnormal mortality for unoperated duodenal ulcer patients after first 5 years. Excess mortality after gastrojejunostomy but slightly below expectation after resection.

Other cancers of digestive system No definitely abnormal mortality

Cancers of pharynx, larynx, and lung Excess mortality for both ulcer sites and for both operated and unoperated patients.

Leukaemia and aleukaemia Excess for unoperated, but not for operated patients.

All other malignant tumours Duodenal ulcer patients showed an excess mortality for which no single localization could be held responsible.

Diabetes Suggestion of subnormal mortality but inconclusive data.

Apoplexy Excess for gastric ulcer less than expected for duodenal ulcer patients.

Coronary heart disease No definitely abnormal mortality but for duodenal ulcer there is a suggestion of deficit among unoperated and excess among operated patients.

Valvular heart disease and other diseases of cardio-vascular system Mortality as expected from these causes combined

Pneumonia No definitely abnormal mortality

Gastro-duodenal ulcer No great difference in mortality ratio between the two sexes or the two ulcer sites, or between resection and gastrojejunostomy

Brus and hernia At most a small increase for operated patients.

Appendicitis No abnormal mortality

Carbuncles of liver Excess for unoperated patients, but interpretation is difficult. No excess for operated patients.

Diseases of bile ducts and gall bladder A very small group There is an excess in operated patients

Suicide Excess for both ulcer sites, operated and unoperated.

Accidents and homicide Excess for operated duodenal ulcer patients.

Multiple sclerosis Mortality not far from expectation.

Amyotrophic lateral sclerosis Excess for unoperated gastric ulcer patients.

## *5 Conclusion*

Peptic ulcer patients who were discharged from the Ullevål Hospital in 1917-39 have later suffered a mortality moderately in excess of the general population.

The pattern of cause of death shows some deviations, mostly minor from that of the general population.

This mortality study has not disclosed late complications of operation to an extent which should influence the indications for operation.

## 6 References

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## *Appendices*



# APPENDIX I

*Various characteristics of the material at start of observation by sex*

## a) AGE AT DISCHARGE

Age at discharge	Number of patients		Total
	Males	Females	
3-9	2		2
10-14	8	4	12
15-19	64	53	117
20-24	263	168	431
25-29	407	160	567
30-34	395	137	532
35-39	366	123	489
40-44	270	112	382
45-49	212	110	322
50-54	144	105	249
55-59	130	92	222
60-64	76	78	154
65-69	49	50	99
70-74	19	32	51
75-79	8	13	21
80 and over	6	6	12
All ages	2,419	1,243	3,662

## b) TIME FROM START OF DYSPEPTIC SYMPTOMS TO DISCHARGE

Duration of dyspepsia	Number of patients		Total
	Males	Females	
No dyspepsia	183	67	250
Less than 3 months	162	71	233
3 months or more, but less than 1 year	227	121	348
1 year or more but less than 5 years	788	310	1,098
5 years or more, but less than 10 years	331	155	486
10 years or more but less than 20 years	310	162	472
20 years or more	158	179	337
Unknown, doubtful	260	178	438
All durations	2,419	1,243	3,662

There was no systematic change in duration of dyspepsia with calendar year of discharge.

## c) PREVIOUS HOSPITAL TREATMENT FOR GASTRIC OR DUODENAL ULCER (Patients previously operated for ulcer have been excluded from the material.)

Hospital treatment prior to registered first stay	Number of patients		Total
	Males	Females	
None	2,163	1,100	3,263
I one of the included departments	16	20	36
In other departments (hospitals)	129	72	201
Doubtful	111	51	162
	2,419	1,243	3,662



# d) HAEMATEMESIS, BY CALENDAR YEAR OF DISCHARGE

Year of discharge	Number of patients					Percentage				
	Haematemesis					Haematemesis				
	None	During stay	Definite history	Doubtful	Total	None	During stay	Definite history	Doubtful	Total
MALES										
1917-19	120	4	42	6	172	69.8	2.3	24.4	3.5	100.0
1920-24	202	11	62	8	283	71.4	3.9	21.9	2.8	100.0
1925-29	281	13	79	16	389	72.2	3.4	20.3	4.1	100.0
1930-34	535	14	99	15	663	80.7	2.1	14.9	2.3	100.0
1935-39	804	8	87	13	912	88.2	0.9	9.5	1.4	100.0
FEMALES										
1917-19	106	11	78	11	207	51.2	5.3	37.7	5.8	100.0
1920-24	132	4	52	17	205	64.4	1.9	25.4	8.3	100.0
1925-29	127	14	55	9	205	62.0	6.8	26.8	4.4	100.0
1930-34	207	11	40	10	268	77.3	4.1	14.9	3.7	100.0
1935-39	508	5	39	6	558	86.0	1.4	10.9	1.7	100.0

# e) MELAENA, BY CALENDAR YEAR OF DISCHARGE

Year of discharge	Number of patients					Percentage				
	None	During stay	Definite history	Doubtful	Total	None	During stay	Definite history	Doubtful	Total
MALES										
1917-19	93	35	13	31	172	54.1	20.3	7.6	18.0	100.0
1920-24	163	47	29	44	283	57.6	16.6	10.3	15.5	100.0
1925-29	236	86	29	38	389	60.7	22.1	7.4	9.8	100.0
1930-34	457	128	48	30	663	68.9	19.3	7.3	4.5	100.0
1935-39	714	112	53	33	912	78.3	12.3	5.8	3.6	100.0
FEMALES										
1917-19	110	45	10	42	207	53.2	21.7	4.8	20.3	100.0
1920-24	118	29	16	42	205	57.6	14.1	7.8	20.5	100.0
1925-29	101	49	17	38	205	49.3	23.9	8.3	18.5	100.0
1930-34	192	39	20	17	268	71.6	14.6	7.5	6.3	100.0
1935-39	285	47	18	8	358	79.6	13.1	5.0	2.3	100.0

# f) ACIDITY ('FREE ACID') AT EWALD'S TEST MEAL DURING STAY BY CALENDAR YEAR OF DISCHARGE

Year of discharge	Number of patients				Percentage					
	None	Free acid ≥ 40	> 40	Not exam.	Total	None	Free acid ≥ 40	> 40	Not exam.	Total
MALES										
1917-19	12	53	42	63	172	7.0	30.8	24.4	37.8	100.0
1920-24	4	84	79	116	283	1.4	29.7	27.9	41.0	100.0
1925-29	8	84	119	178	389	2.0	21.6	30.6	45.8	100.0
1930-34	9	141	249	264	663	1.4	21.3	37.5	39.8	100.0
1935-39	16	213	440	243	912	1.8	23.4	48.1	26.7	100.0
FEMALES										
1917-19	8	79	27	93	207	3.9	38.2	13.0	44.9	100.0
1920-24	13	89	22	81	205	6.4	43.4	10.7	39.5	100.0
1925-29	8	67	42	88	205	3.9	32.7	20.5	42.9	100.0
1930-34	8	112	64	84	268	3.0	41.8	23.9	31.3	100.0
1935-39	10	150	119	79	358	2.8	41.9	33.2	22.1	100.0

# **g) X RAY EXAMINATION OF STOMACH PRIOR TO ADMISSION BY CALENDAR YEAR OF DISCHARGE**

STOMACH PRIOR TO ADMISSION BY GILENT									
YEAR OF DISCHARGE		Number of patients X-ray examination			Total	Percentage X-ray examination			Total
Year of discharge	Yes	No	Doubtful	Yes		No	Doubtful		
MALES									
1917-19	6	166	0	172	3.5	96.5	0.0	100.0	
1920-24	10	261	12	283	3.6	92.2	4.2	100.0	
1925-29	43	297	52	389	11.5	73.1	13.4	100.0	
1930-34	219	380	64	663	33.0	57.3	9.7	100.0	
1935-39	480	369	63	912	52.6	40.5	6.9	100.0	
FEMALES									
1917-19	1	193	7	207	0.5	96.1	3.4	100.0	
1920-24	12	186	7	205	5.9	90.7	3.4	100.0	
1925-29	28	152	23	203	13.7	74.1	12.2	100.0	
1930-34	79	157	32	268	29.5	58.6	11.9	100.0	
1935-39	177	159	22	358	49.4	44.4	6.2	100.0	
Includes patients who were examined, but with unknown results.									
b) X RAY EXAMINATION DURING FIRST REGISTERED YEAR OF DISCHARGE									
Number of patients examined									
Year of discharge									
1917-19									
1920-24									
1925-29									
1930-34									
1935-39									

Includes patients who were examined, but with unknown results.

## **h) X RAY EXAMINATION DURING FIRST REGISTERED STAY BY CALENDAR YEAR OF DISCHARGE**

Year of discharge	Number of patients Examined			Total	Percentage Examined				Total
	Yes	No	Doubtful		Ulcer demonstrated			Not examined	
					Yes	No	Doubtful		
<b>MALES</b>									
1917-19	1	47	0	124	.6	27.3	.0	72.1	100.0
1920-24	12	91	58	122	4.2	32.2	20.5	43.1	100.0
1925-29	19	77	68	205	4.9	19.8	22.6	52.7	100.0
1930-34	180	68	224	663	28.5	10.3	33.8	27.4	100.0
1935-39	369	123	205	912	40.5	13.5	22.5	23.5	100.0
<b>FEMALES</b>									
1917-19	8	27	4	168	3.9	13.0	1.9	61.2	100.0
1920-24	11	64	39	205	5.4	31.2	19.0	44.4	100.0
1925-29	13	43	41	205	7.3	21.0	20.0	51.7	100.0
1930-34	94	50	83	268	35.1	18.7	31.7	14.5	100.0
1935-39	184	32	69	358	51.4	14.5	19.3	14.8	100.0

1) OTHER CONDITIONS MENTIONED AS DISCHARGE DIAGNOSIS

Discharge diagnosis other than ulcer	Number of patients	Percentage
Diarrhea, including symptoms of ulcer	1	0.1
hematemesis	1	0.1
melena	1	0.1
presence of cancer indicated	1	0.1
perforated duodenum	1	0.1
pyloric stenosis	1	0.1
pyloric obstruction	1	0.1
pyloric ulcer	1	0.1
pyloric stenosis	1	0.1
pyloric obstruction	1	0.1
pyloric ulcer	1	0.1
pyloric stenosis	1	0.1
pyloric obstruction	1	0.1
pyloric ulcer	1	0.1
pyloric stenosis	1	0.1
pyloric obstruction	1	0.1
pyloric ulcer	1	0.1
pyloric stenosis	1	0.1
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pyloric ulcer	1	0.1
pyloric stenosis	1	0.1
pyloric obstruction	1	0.1
pyloric ulcer	1	0.1
pyloric stenosis	1	0.1
pyloric obstruction	1	0.1
pyloric ulcer	1	0.1
pyloric stenosis	1	0.1
pyloric obstruction	1	0.1
pyloric ulcer	1	0.1
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pyloric ulcer	1	0.1
pyloric stenosis	1	0.1
pyloric obstruction	1	0.1
pyloric ulcer	1	0.1
pyloric stenosis	1	0.1

## **i) OTHER CONDITIONS MENTIONED AS DISCHARGE DIAGNOSES**

Discharge diagnoses other than ulcer such as:  
 None, including symptoms of ulcer  
 haematemesis  
 Possibility of cancer indicated  
 Heart disease and/or hypertension  
 Tuberculosis of lungs, active or unspecified  
 Inactive tuberculosis of lungs, or unspecified lung infiltration  
 Other conditions

	MALES	FEMALES	Total
None, including symptoms of ulcer	2,281	1,128	3,409
haematemesis	10	8	18
Possibility of cancer indicated	21	16	37
Heart disease and/or hypertension	5	3	8
Tuberculosis of lungs, active or unspecified	3	3	6
Inactive tuberculosis of lungs, or unspecified lung infiltration	99	85	184
Other conditions	2,419	1,243	3,662

## Definition of groups of causes of death

		Code numbers in			
		1917-26	1927-40	1941-50	1951-57
1	Tuberculosis of resp. system	33	1400	1121-1123	001-009
2	Other forms of tuberculosis	34-41 124	1410-1470 2410	1131-1139	010-019
3	Syphilis	43-44 61 65, 78	1520-1521 2620	1181-1185	020-029
4	Influenza	18	2700 3041		
			1120-1121	1201-1202	480-483
5	Other infectious and parasitic diseases	8-16, 19, 21 23 26-28, 30-32, 42, 45	1000-1110 1130-1140, 1160-1190 1210-1310 1310 1540-1600	1000-1110 1140-1150, 1190, 1210-1292 1310 2690	030-138
6	Cancer of oesophagus	part of 102	7006	1410	150
7	Cancer of stomach	101	7010	1411	151
8	Other cancers of dig. organs	part of 102	7021-7025	1412-1415	152-157
9	Cancer of pharynx	part of 105	7005	1405-1408	155-148
10	Cancer of larynx	part of 105	7026	1421	161
11	Cancer of lung	part of 105	7027	1422	162
12	Leukemia and leukemia	51	2010	1840	904
13	All other malignant tumours	100 108-104 part of 105, 106-108	1500, 7001-7004 7028- 7060 7500-7550	1300 1401-1404 1407- 1409 1416-1419 1425- 1493	140-144 158-159 163-203, 205
14	Diabetes mellitus	50	2560	1650	260
15	Psychoses	62	2750	2070	300-309
16	Chronic alcoholism	57	8000	1902	322.1 322.2
17	Apoplexy	59	2600	2040-2060	330-334
18	Coronary heart disease	71	3080	2230-2240	420, 422
19	Valvular heart disease	70	3020	2270	410-414 421
20	Other diseases of cardiovascular system	20 69 72 75, 111	1200, 3000-3010, 3040, 3042, 3050-3070	1600 2200-2210, 2250-2310	400-402 415-416, 430-458
21	Sudden death - heart paralysis	74	9000	4200	782 4 795.2
22	Pneumonia	17 79	3520-3530	2410-2430	490-493
23	Bronchitis and asthma	76-78	3500-3510 3570	2400 2460	241 500-502
24	Other dis. of respiratory organs	80-84	3540-3560 3580-3590	2440-2450, 2470-2510	470-475, 510-527
25	Gastro-duodenal ulcer	86	4000-4010	2610	540-542

# APPENDIX II (cont.)

		Code numbers in:				
		1917 III	1927-40	1931-50	1951-57	
26.	Acute and chronic gastric catarrh	29 85	1150, 4020	2670-2680	515-571	
27	Teus and hernia	80-90	4050-4060	2690-2700	500-501 570	
28.	Appendicitis	87	4040	2640	550-553	
29.	Cirrhosis of liver	92	4110	2640	581	
30.	Diseases of bile ducts and gall bladder	91	4120-4130	2710-2720	501-505	
31	Other diseases of digestive organs	88(93)	4080, 4070-4100, 4140-4,000	2680, 2700 2730-2750 2680	530-539 571-573 572-580 582 583, 587	
32	Nephritis	94-95	5000-5010	2800-2820	500-511	
33.	Other diseases of urinary and genital organs	96-99	5020-5010, 5200 5210	2790 2930	600-637	
34	Complications of pregnancy childbirth and puerperium	24 113-121	5500-5700	3000-3100	640-689	
35.	Diseases of skin, cellular tissue bones, and organs of movement	40 110 112	6000-6020 6,000-6120	3110 3200-3220, 3300 3310	690-710	
36.	Senility	6	6500	3500	734	
37	Scalds	137	8700-8799	3600 3670	740-747	
38.	Accidents and homicide	178-179	8800-8899 8800-8900	3700-4111	7500-815 8,800-9999	
39.	Other and unknown causes	1 5, 7 46, 48, 49 5, -6, -8, 60 63, 64 66, 68, 104, 122, 123 125, 126, 130	0000-0100 0100, 2000 2030-2050 2,000-23,00, 2370-2400, 2470-2500, 2610 2630-2660, 2800-2810, 2700, 3010-3200, 3400, 4 10 5010	1507 1512 1620 1640 1760 1800-1830 19,40 1960, 1901 1911 1922 2000-2030 2080 2120 3100, 4 10	210-239 240 242-250 270-299 310 322,0, 323-326 340, 348, 750-759, 780-782, 790-793, 793,0-793,1 799,3-799,5	

Notes: 1 For 1917 III rates for cancers of oesophagus, pharynx, larynx and lung have been based on the supplementary list submitted by the Health Officers. Deaths among ulcer patients in this period have been referred to one of the four cancer types if so indicated by the certificate.

2 For the years prior to 1928, when the total number of deaths in Norway exceeded the number included in the cause-of-death tables, the Institut has added the difference: Other and unknown causes.

3 The code numbers for the period 1911-40 are the working numbers used in the Central Bureau of Statistics and not the numbers used in the Medical Statistical Reports.

4 Some of the deaths which occurred outside Norway during the second world war have not been included in the cause-of-death tables in the Medical Statistical Reports. The Institute has added these deaths to Accidents and homicide.

5. In 1927-40 and 1941-50 total of 8 deaths occurred among the ulcer patients where neither cause code nor any other information on cause of death has been found. These deaths have been counted in the group Other and unknown causes.

Officially coded to group	1	2	3	4	5	6	7	8	9	10	11	12	13
1 Tuberculosis of resp. syst.	83												
2 Other forms of tuberculosis	1	4					1						
3 Syphilis			11										
4 Influenza				2									
5 Other infect. diseases					9								
6 Cancer of oesophagus						5	3						
7 Cancer of stomach							97	2			1		
8 Other cancers of digest. org							1	30		1			
9 Cancer of pharynx									3				
10 Cancer of larynx									1	4			
11 Cancer of lung							1				21		
12 Leukaemia and aleukaemia												11	
13 All other malign. tumours								3					75
14 Diabetes mellitus													
15 Psychoses													
16 Chronic alcoholism													
17 Apoplexy											1		3
18 Coronary heart disease				2									
19 Valvular heart disease		1	2										
20 Other dis. of card. vasc. system			1										1
21 Sudden death - heart paralysis			1										
22 Pneumonia	4							1					
23 Bronchitis and asthma													
24 Other dis. of resp. syst.			1					1					
25 Gastro-duodenal ulcer							1						
26 Ac. and chr. gastric catarrh													
27 Piles and haemorrhoids													
28 Appendicitis													1
29 Cirrhosis of liver											1		
30 Dis. of bile ducts							1						1
31 Other dis. of digest. org					2		1						1
32 Nephritis													
33 Other dis. of urin. org							1						2
34 Compl. of pregnancy													
35 Diseases of skin.													
36 Senility													
37 Suicide													
38 Accidents and homicide													
39 Other and unknown causes	1				1		3	2			2		2
All causes	89	5	18	2	12	5	110	39	4	5	26	11	96

### III

distributed by official code and revised code  
in Appendix II

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$\mathcal{L}^{\infty}$  norm of the error function defined = Approach 1 and for  $\mathcal{L}^2$  norm

$\mu$	M.L.D.
$\mu = \pi^T - \{D_1 + D_2 + D_3 + D_4\}$	

...<sup>22</sup> וְהָיָה כִּי יִשְׁמַע ה' אֶת הַקּוֹל וְהָיָה

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|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 |
|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|

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|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|----|----|----|----|----|----|----|----|----|----|-----|
| 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 |    |    |    |    |    |    |    |    |    |    |     |
| 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89  | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 |

# APPENDIX IV (cont.)

| MALES                                      |       |       |       |       |       |      |       | FEMALES |       |       |       |       |       |      |  |
|--|-------|-------|-------|-------|-------|------|-------|---------|-------|-------|-------|-------|-------|------|--|
| 20-29                                      | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+  |       | 20-29   | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+  |  |
| 5. Other infectious and parasitic diseases |       |       |       |       |       |      |       |         |       |       |       |       |       |      |  |
| 1917-21                                    | .272  | .206  | .234  | .312  | .422  | .584 | .944  | .252    | .202  | .197  | .251  | .219  | .402  | .558 |  |
| 1922-26                                    | .178  | .154  | .193  | .248  | .306  | .438 | .438  | .134    | .141  | .134  | .168  | .187  | .250  | .406 |  |
| 1927-30                                    | .204  | .192  | .226  | .287  | .408  | .531 | .515  | .156    | .162  | .141  | .217  | .246  | .338  | .468 |  |
| 1931-35                                    | .175  | .196  | .207  | .220  | .373  | .391 | .517  | .118    | .125  | .127  | .174  | .239  | .286  | .435 |  |
| 1936-40                                    | .136  | .148  | .185  | .211  | .310  | .428 | .663  | .109    | .108  | .104  | .177  | .203  | .339  | .704 |  |
| 1941-45                                    | .296  | .215  | .227  | .300  | .355  | .531 | 1.109 | .271    | .188  | .194  | .269  | .311  | .511  | .892 |  |
| 1946-50                                    | .032  | .074  | .087  | .091  | .141  | .169 | .491  | .066    | .052  | .066  | .077  | .145  | .225  | .547 |  |
| 1951-57                                    | .055  | .053  | .048  | .047  | .055  | .129 | .292  | .014    | .031  | .025  | .047  | .049  | .102  | .310 |  |

## 6. Cancer of oesophagus

|         |      |      |      |      |      |      |      |      |      |      |      |      |      |      |  |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|--|
| 1917-21 | .002 | -    | .005 | .003 | .239 | .366 | .258 | -    | .004 | .014 | .038 | .094 | .129 | .068 |  |
| 1922-26 | -    | .005 | .029 | .102 | .290 | .519 | .296 | .001 | .006 | .011 | .029 | .111 | .217 | .155 |  |
| 1927-30 | -    | .003 | .029 | .101 | .290 | .589 | .716 | -    | .001 | .005 | .053 | .120 | .303 | .357 |  |
| 1931-35 | .001 | .006 | .018 | .121 | .324 | .376 | .735 | -    | .005 | .012 | .051 | .158 | .260 | .427 |  |
| 1936-40 | -    | -    | .020 | .118 | .289 | .589 | .804 | .001 | -    | .010 | .052 | .088 | .217 | .329 |  |
| 1941-45 | -    | .001 | .024 | .087 | .263 | .442 | .702 | -    | .002 | .014 | .017 | .072 | .181 | .307 |  |
| 1946-50 | -    | .004 | .008 | .050 | .225 | .306 | .830 | -    | .002 | .003 | .024 | .072 | .138 | .226 |  |
| 1951-57 | -    | .003 | .011 | .047 | .148 | .401 | .427 | -    | .002 | .002 | .006 | .053 | .123 | .244 |  |

## 7. Cancer of stomach

|         |      |      |      |       |       |       |       |      |      |      |       |       |       |       |  |
|---------|------|------|------|-------|-------|-------|-------|------|------|------|-------|-------|-------|-------|--|
| 1917-21 | .010 | .108 | .491 | 1.637 | 3.636 | 4.976 | 3.860 | .014 | .072 | .404 | 1.039 | 2.078 | 3.433 | 3.045 |  |
| 1922-26 | .008 | .118 | .476 | 1.617 | 3.596 | 5.892 | 5.128 | .011 | .073 | .355 | 1.046 | 2.362 | 4.092 | 3.909 |  |
| 1927-30 | .006 | .089 | .396 | 1.225 | 3.371 | 5.536 | 5.934 | .013 | .084 | .310 | .787  | 2.220 | 4.222 | 4.806 |  |
| 1931-35 | .006 | .067 | .404 | 1.320 | 3.203 | 5.927 | 6.602 | .010 | .066 | .251 | .722  | 1.972 | 4.146 | 5.521 |  |
| 1936-40 | .008 | .058 | .311 | 1.131 | 2.858 | 5.807 | 7.184 | .008 | .054 | .230 | .614  | 1.723 | 4.174 | 5.732 |  |
| 1941-45 | .007 | .054 | .251 | .831  | 2.299 | 5.141 | 5.971 | .007 | .050 | .177 | .518  | 1.468 | 3.410 | 5.150 |  |
| 1946-50 | .006 | .049 | .223 | .792  | 2.088 | 4.923 | 7.368 | .003 | .043 | .161 | .445  | 1.214 | 3.018 | 5.528 |  |
| 1951-57 | .006 | .035 | .206 | .647  | 1.872 | 3.937 | 6.000 | .002 | .042 | .123 | .532  | .889  | 2.449 | 4.835 |  |

## 8. Other cancers of digestive organs

|         |      |      |      |      |      |       |       |      |      |      |      |      |       |       |  |
|---------|------|------|------|------|------|-------|-------|------|------|------|------|------|-------|-------|--|
| 1917-21 | .005 | .024 | .102 | .357 | .864 | 1.207 | 1.089 | .005 | .027 | .131 | .337 | .571 | 1.104 | 1.008 |  |
| 1922-26 | .005 | .033 | .107 | .327 | .843 | 1.327 | 1.306 | .008 | .034 | .115 | .313 | .670 | 1.227 | .948  |  |
| 1927-30 | .002 | .028 | .069 | .282 | .918 | 1.421 | 1.433 | .001 | .024 | .102 | .293 | .670 | 1.514 | 1.505 |  |
| 1931-35 | .007 | .025 | .106 | .396 | .896 | 1.622 | 2.158 | .005 | .023 | .107 | .310 | .773 | 1.465 | 2.075 |  |
| 1936-40 | .008 | .034 | .108 | .393 | .918 | 1.953 | 2.434 | .003 | .025 | .115 | .318 | .693 | 1.629 | 2.082 |  |
| 1941-45 | .005 | .023 | .111 | .329 | .970 | 2.100 | 2.634 | .009 | .023 | .080 | .330 | .811 | 1.782 | 2.689 |  |
| 1946-50 | .004 | .040 | .110 | .346 | .924 | 2.043 | 3.093 | .005 | .024 | .106 | .328 | .780 | 1.717 | 3.166 |  |
| 1951-57 | .007 | .025 | .108 | .383 | .969 | 2.136 | 2.904 | .006 | .027 | .107 | .320 | .738 | 1.731 | 2.902 |  |



# APPENDIX IV (cont.)

|                     | MALES |       |       |       |       |       |      | FEMALES |       |       |       |       |       |      |
|---------------------|-------|-------|-------|-------|-------|-------|------|---------|-------|-------|-------|-------|-------|------|
|                     | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+  | 20-29   | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+  |
| 9 Cancer of pharynx |       |       |       |       |       |       |      |         |       |       |       |       |       |      |
| 1917-21             | .002  | -     | .003  | .003  | .045  | .024  | .047 | -       | -     | -     | .009  | -     | .019  | .017 |
| 1922-26             | -     | .001  | .003  | .012  | .021  | .031  | .027 | -       | -     | -     | .009  | .002  | .011  | .019 |
| 1927-30             | -     | .005  | .002  | .011  | .006  | .068  | .047 | .001    | -     | .006  | .016  | .016  | .012  | .033 |
| 1931-35             | .001  | -     | .003  | .019  | .041  | .048  | .046 | .001    | .001  | .004  | .009  | .016  | .016  | .049 |
| 1936-40             | .002  | -     | .006  | .016  | .032  | .054  | .054 | .002    | .002  | .003  | .013  | .017  | .018  | .046 |
| 1941-45             | -     | .001  | .008  | .018  | .030  | .064  | .092 | -       | .001  | .001  | .009  | .017  | .011  | .029 |
| 1946-50             | -     | -     | .005  | .017  | .033  | .041  | .036 | .001    | .001  | .003  | .011  | .022  | .023  | .082 |
| 1951-57             | -     | .001  | .006  | .017  | .054  | .074  | .124 | -       | .001  | .004  | .015  | .021  | .037  | .079 |

|                      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
|----------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 10. Cancer of larynx |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| 1917-21              | -    | -    | .003 | .017 | .032 | .040 | -    | -    | -    | -    | .006 | .011 | -    | -    |
| 1922-26              | -    | -    | .002 | .022 | .021 | .054 | .067 | -    | .002 | .001 | .009 | .019 | .036 | -    |
| 1927-30              | -    | -    | .006 | .016 | .043 | .068 | .031 | -    | -    | .003 | .008 | .013 | .016 | .067 |
| 1931-35              | -    | .002 | .011 | .022 | .031 | .068 | .138 | -    | .002 | .002 | .015 | .022 | .031 | .016 |
| 1936-40              | .001 | .001 | .002 | .014 | .063 | .080 | .097 | -    | .001 | .003 | .010 | .019 | .033 | .061 |
| 1941-45              | -    | -    | .003 | .017 | .046 | .086 | .081 | .001 | -    | .005 | .010 | .010 | .031 | .036 |
| 1946-50              | -    | -    | .007 | .016 | .046 | .069 | .107 | -    | .001 | .003 | .006 | .024 | .023 | .006 |
| 1951-57              | -    | .001 | .003 | .014 | .025 | .060 | .107 | -    | -    | -    | .001 | .002 | .006 | .012 |

|                   |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
|-------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 11 Cancer of lung |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| 1917-21           | .002 | -    | .019 | .010 | .023 | .032 | -    | -    | .002 | .010 | .012 | .008 | .019 | -    |
| 1922-26           | -    | .004 | .003 | .022 | .034 | .031 | -    | .003 | .003 | .007 | .021 | .041 | .014 | -    |
| 1927-30           | .002 | .004 | .011 | .039 | .051 | .047 | .047 | -    | .001 | .018 | .026 | .018 | .016 | .011 |
| 1931-35           | .001 | .009 | .021 | .038 | .075 | .068 | .034 | -    | .003 | .014 | .036 | .057 | .033 | .057 |
| 1936-40           | .002 | .010 | .018 | .065 | .114 | .172 | .182 | .001 | .006 | .013 | .041 | .094 | .116 | .054 |
| 1941-45           | .004 | .008 | .042 | .097 | .180 | .193 | .153 | .001 | .008 | .028 | .066 | .106 | .150 | .121 |
| 1946-50           | .002 | .015 | .065 | .166 | .277 | .362 | .259 | .001 | .008 | .025 | .073 | .145 | .169 | .157 |
| 1951-57           | .003 | .009 | .064 | .272 | .401 | .199 | .202 | .001 | .003 | .012 | .049 | .091 | .123 | .070 |

|                             |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
|-----------------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 12 Leukaemia and aleukaemia |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| 1917-21                     | .007 | .019 | .008 | .021 | .033 | .024 | .014 | .005 | .006 | .009 | .016 | .027 | .004 | -    |
| 1922-26                     | .010 | .004 | .019 | .030 | .030 | .031 | -    | .006 | .006 | .018 | .028 | .028 | .014 | -    |
| 1927-30                     | .009 | .022 | .015 | .044 | .045 | .026 | -    | .011 | .003 | .013 | .012 | .024 | .016 | .022 |
| 1931-35                     | .011 | .006 | .024 | .032 | .036 | .032 | .034 | .006 | .008 | .016 | .035 | .028 | .019 | -    |
| 1936-40                     | .015 | .015 | .024 | .038 | .071 | .046 | .054 | .009 | .014 | .016 | .046 | .054 | .056 | -    |
| 1941-45                     | .017 | .014 | .037 | .066 | .116 | .118 | .051 | .013 | .010 | .021 | .038 | .080 | .079 | .043 |
| 1946-50                     | .024 | .024 | .039 | .087 | .148 | .200 | .098 | .017 | .014 | .019 | .069 | .084 | .141 | .057 |
| 1951-57                     | .022 | .028 | .043 | .107 | .219 | .333 | .202 | .017 | .024 | .042 | .082 | .136 | .202 | .124 |

## APPENDIX IV (cont.)

| MALES |       |       |       |       |       |     | FEMALES |       |       |       |       |       |     |
|-------|-------|-------|-------|-------|-------|-----|---------|-------|-------|-------|-------|-------|-----|
| 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ | 20-29   | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ |

## 13. All other malignant tumours

|         |      |      |      |      |       |       |       |      |      |      |       |       |       |       |
|---------|------|------|------|------|-------|-------|-------|------|------|------|-------|-------|-------|-------|
| 1917-21 | .040 | .051 | .158 | .403 | .897  | 1.871 | 2.563 | .036 | .201 | .629 | 1.044 | 1.520 | 1.735 | 1.932 |
| 1922-26 | .055 | .066 | .178 | .411 | 1.215 | 2.285 | 3.258 | .056 | .194 | .769 | 1.292 | 1.709 | 2.131 | 2.400 |
| 1927-30 | .054 | .072 | .191 | .491 | 1.249 | 2.650 | 3.800 | .055 | .218 | .739 | 1.322 | 1.812 | 2.493 | 2.855 |
| 1931-35 | .057 | .069 | .161 | .462 | 1.225 | 2.731 | 4.247 | .051 | .209 | .742 | 1.434 | 1.921 | 2.580 | 3.726 |
| 1936-40 | .057 | .074 | .181 | .411 | 1.239 | 2.863 | 4.921 | .043 | .196 | .660 | 1.382 | 1.909 | 2.791 | 3.842 |
| 1941-45 | .068 | .069 | .188 | .537 | 1.347 | 3.422 | 5.258 | .050 | .197 | .666 | 1.371 | 2.029 | 2.931 | 4.230 |
| 1946-50 | .069 | .102 | .193 | .514 | 1.415 | 3.728 | 6.466 | .075 | .219 | .680 | 1.380 | 2.143 | 3.511 | 5.152 |
| 1951-57 | .110 | .152 | .285 | .681 | 1.604 | 4.294 | 7.437 | .032 | .252 | .703 | 1.581 | 2.368 | 3.799 | 5.055 |

## 14 Diabetes mellitus

|         |      |      |      |      |      |      |       |      |      |      |      |      |       |       |
|---------|------|------|------|------|------|------|-------|------|------|------|------|------|-------|-------|
| 1917-21 | .060 | .072 | .032 | .203 | .282 | .409 | .417  | .056 | .045 | .075 | .158 | .316 | .359  | .225  |
| 1922-26 | .049 | .059 | .071 | .156 | .312 | .528 | .563  | .041 | .041 | .075 | .190 | .328 | .560  | .406  |
| 1927-30 | .023 | .034 | .075 | .115 | .401 | .620 | .561  | .027 | .025 | .063 | .186 | .465 | .914  | .446  |
| 1931-35 | .033 | .031 | .030 | .090 | .332 | .676 | .510  | .019 | .020 | .041 | .141 | .485 | .979  | .861  |
| 1936-40 | .020 | .019 | .023 | .105 | .311 | .811 | .963  | .012 | .011 | .032 | .127 | .548 | 1.136 | 1.079 |
| 1941-45 | .011 | .019 | .032 | .117 | .279 | .717 | .844  | .013 | .017 | .028 | .081 | .371 | 1.047 | 1.077 |
| 1946-50 | .012 | .021 | .019 | .036 | .303 | .810 | 1.106 | .016 | .018 | .029 | .074 | .461 | 1.577 | 1.897 |
| 1951-57 | .022 | .033 | .056 | .059 | .152 | .381 | .657  | .026 | .025 | .016 | .058 | .209 | .533  | .869  |

## 15 Psychoses

|         |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 1917-21 | .027 | .003 | .086 | .139 | .183 | .204 | .236 | .024 | .000 | .094 | .146 | .201 | .209 | .315 |
| 1922-26 | .031 | .059 | .071 | .094 | .148 | .291 | .283 | .024 | .046 | .068 | .107 | .147 | .221 | .358 |
| 1927-30 | .007 | .022 | .029 | .025 | .057 | .032 | 1.5  | .004 | .018 | .016 | .034 | .060 | .128 | .212 |
| 1931-35 | .005 | .013 | .022 | .044 | .034 | .048 | .046 | .008 | .016 | .031 | .068 | .051 | .063 | .057 |
| 1936-40 | .006 | .010 | .021 | .021 | .022 | .046 | .021 | .005 | .011 | .022 | .029 | .045 | .074 | .060 |
| 1941-45 | .009 | .015 | .021 | .027 | .078 | .021 | .010 | .004 | .008 | .024 | .038 | .041 | .045 | .029 |
| 1946-50 | .007 | .006 | .014 | .019 | .031 | .025 | .036 | .005 | .013 | .021 | .035 | .045 | .026 | .019 |
| 1951-57 | .009 | .010 | .018 | .023 | .046 | .146 | .534 | .005 | .005 | .011 | .026 | .058 | .176 | .803 |

## 16. Chronic alcoholism

|         |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 1917-21 | .002 | .004 | .012 | .011 | .003 | .005 | -    | -    | -    | .001 | -    | -    | -    | -    |
| 1922-26 | .002 | .018 | .026 | .018 | .018 | .009 | -    | .001 | -    | .001 | .002 | .004 | -    | -    |
| 1927-30 | .003 | .013 | .022 | .048 | .022 | .003 | .016 | -    | .003 | -    | -    | .003 | -    | -    |
| 1931-35 | .002 | .005 | .009 | .026 | .015 | .003 | -    | -    | -    | .001 | .002 | -    | -    | -    |
| 1936-40 | -    | .004 | .014 | .015 | .011 | .013 | -    | -    | -    | -    | .001 | .002 | -    | .008 |
| 1941-45 | .001 | .002 | .009 | .011 | .010 | .007 | -    | -    | -    | .001 | -    | .002 | .003 | -    |
| 1946-50 | -    | .002 | .008 | .022 | .018 | .006 | -    | -    | -    | .002 | -    | .002 | -    | .006 |
| 1951-57 | .001 | .003 | .007 | .014 | .012 | .010 | -    | -    | -    | .001 | .001 | .001 | -    | -    |

# APPENDIX IV (cont.)

| MALES |       |       |       |       |       |     |  | FEMALES |       |       |       |       |       |     |  |
|-------|-------|-------|-------|-------|-------|-----|--|---------|-------|-------|-------|-------|-------|-----|--|
| 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ |  | 20-29   | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ |  |

## 17 Apoplexy

|         |      |      |      |       |       |       |        |      |      |      |       |       |        |        |  |
|---------|------|------|------|-------|-------|-------|--------|------|------|------|-------|-------|--------|--------|--|
| 1917-21 | .018 | .077 | .234 | .979  | 2.870 | 6.937 | 12.274 | .018 | .066 | .261 | .936  | 2.718 | 7.019  | 11.033 |  |
| 1922-26 | .015 | .058 | .231 | 1.022 | 2.942 | 7.877 | 13.528 | .015 | .050 | .259 | 1.045 | 3.060 | 7.532  | 13.005 |  |
| 1927-30 | .010 | .057 | .258 | .862  | 2.933 | 8.630 | 17.367 | .010 | .044 | .235 | .907  | 3.114 | 8.107  | 16.447 |  |
| 1931-35 | .014 | .041 | .212 | .790  | 2.922 | 8.443 | 17.483 | .009 | .045 | .229 | 1.016 | 3.024 | 8.455  | 17.351 |  |
| 1936-40 | .013 | .046 | .178 | .776  | 2.914 | 8.388 | 19.590 | .011 | .029 | .257 | .982  | 2.936 | 8.624  | 19.500 |  |
| 1941-45 | .022 | .046 | .153 | .630  | 2.431 | 7.437 | 19.837 | .021 | .047 | .160 | .811  | 2.677 | 7.810  | 19.732 |  |
| 1946-50 | .024 | .036 | .157 | .619  | 2.639 | 8.575 | 21.693 | .012 | .039 | .158 | .786  | 2.795 | 9.244  | 22.780 |  |
| 1951-57 | .017 | .033 | .140 | .564  | 2.513 | 9.649 | 28.353 | .012 | .033 | .143 | .650  | 2.525 | 10.168 | 29.903 |  |

## 18. Coronary heart disease

|         |      |      |      |       |       |        |        |      |      |      |      |       |       |        |  |
|---------|------|------|------|-------|-------|--------|--------|------|------|------|------|-------|-------|--------|--|
| 1917-21 | .009 | .018 | .064 | .194  | .679  | 1.324  | 1.264  | .007 | .022 | .081 | .163 | .635  | 1.241 | 1.279  |  |
| 1922-26 | .019 | .024 | .133 | .363  | .827  | 1.699  | 2.100  | .012 | .020 | .089 | .268 | .664  | 1.508 | 1.906  |  |
| 1927-30 | .011 | .030 | .121 | .344  | 1.061 | 2.104  | 2.601  | .017 | .028 | .076 | .219 | .685  | 1.850 | 2.587  |  |
| 1931-35 | .013 | .033 | .139 | .402  | 1.467 | 3.269  | 4.707  | .010 | .029 | .089 | .290 | .972  | 2.919 | 4.717  |  |
| 1936-40 | .014 | .043 | .147 | .334  | 1.785 | 4.500  | 8.610  | .012 | .034 | .089 | .400 | 1.288 | 4.064 | 8.166  |  |
| 1941-45 | .017 | .033 | .193 | .671  | 1.964 | 5.227  | 12.103 | .017 | .021 | .096 | .347 | 1.266 | 4.218 | 10.301 |  |
| 1946-50 | .008 | .024 | .241 | .842  | 2.768 | 6.808  | 13.228 | .009 | .022 | .068 | .311 | 1.526 | 5.207 | 12.251 |  |
| 1951-57 | .016 | .073 | .470 | 1.924 | 5.126 | 12.426 | 26.403 | .005 | .015 | .070 | .450 | 2.234 | 8.435 | 24.212 |  |

## 19. Valvular heart disease

|         |      |      |      |      |       |       |       |      |      |      |      |       |       |       |  |
|---------|------|------|------|------|-------|-------|-------|------|------|------|------|-------|-------|-------|--|
| 1917-21 | .147 | .203 | .381 | .772 | 1.662 | 3.247 | 3.035 | .159 | .257 | .448 | .824 | 1.822 | 3.639 | 5.431 |  |
| 1922-26 | .117 | .154 | .333 | .775 | 1.717 | 3.411 | 3.42  | .135 | .18  | .404 | .839 | 2.052 | 5.953 | 4.200 |  |
| 1927-30 | .116 | .156 | .372 | .935 | 1.985 | 4.067 | 4.922 | .098 | .193 | .427 | .840 | 2.225 | 4.861 | 5.999 |  |
| 1931-35 | .072 | .124 | .32  | .757 | 1.927 | 4.033 | 3.396 | .073 | .163 | .384 | .773 | 1.862 | 4.862 | 7.093 |  |
| 1936-40 | .048 | .117 | .231 | .820 | 1.373 | 3.758 | 6.283 | .062 | .126 | .243 | .601 | 1.684 | 4.524 | 7.500 |  |
| 1941-45 | .023 | .068 | .134 | .335 | .886  | 2.000 | 2.889 | .027 | .058 | .153 | .355 | .957  | 2.400 | 5.174 |  |
| 1946-50 | .032 | .043 | .143 | .348 | 1.083 | 3.023 | 2.738 | .019 | .047 | .141 | .335 | 1.031 | 3.489 | 5.133 |  |
| 1951-57 | .011 | .025 | .091 | .168 | .407  | .876  | 1.977 | .010 | .025 | .084 | .184 | .404  | 1.167 | 2.691 |  |

## 20. Other diseases of cardio-vascular system

|         |      |      |      |      |       |       |        |      |      |      |      |       |       |        |  |
|---------|------|------|------|------|-------|-------|--------|------|------|------|------|-------|-------|--------|--|
| 1917-21 | .031 | .058 | .096 | .304 | 1.457 | 6.208 | 11.691 | .064 | .063 | .081 | .262 | .773  | 3.490 | 7.015  |  |
| 1922-26 | .052 | .052 | .091 | .345 | 1.509 | 6.867 | 13.487 | .057 | .046 | .071 | .180 | .883  | 5.977 | 9.715  |  |
| 1927-30 | .062 | .063 | .140 | .337 | 1.631 | 7.104 | 20.093 | .085 | .125 | .182 | .281 | .936  | 4.918 | 14.038 |  |
| 1931-35 | .060 | .058 | .130 | .471 | 1.393 | 7.835 | 25.003 | .062 | .109 | .192 | .302 | 1.034 | 5.296 | 18.278 |  |
| 1936-40 | .035 | .057 | .141 | .428 | 1.601 | 6.413 | 23.375 | .045 | .105 | .145 | .326 | 1.078 | 4.866 | 18.819 |  |
| 1941-45 | .045 | .083 | .139 | .294 | .960  | 4.574 | 20.263 | .036 | .069 | .107 | .216 | .810  | 3.853 | 19.199 |  |
| 1946-50 | .028 | .049 | .108 | .331 | 1.149 | 4.538 | 21.406 | .024 | .046 | .093 | .41  | 1.003 | 3.976 | 22.546 |  |
| 1951-57 | .021 | .032 | .143 | .327 | 1.774 | 5.804 | 19.656 | .021 | .039 | .109 | .418 | 1.663 | 6.599 | 22.564 |  |

# APPENDIX IV (cont)

| MALES |       |       |       |       |       |     |  | FEMALES |       |       |       |       |       |     |  |
|-------|-------|-------|-------|-------|-------|-----|--|---------|-------|-------|-------|-------|-------|-----|--|
| 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ |  | 20-29   | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ |  |

## 21 Sudden death - heart paralysis

|         |      |      |      |      |       |       |       |      |      |      |      |      |       |       |  |
|---------|------|------|------|------|-------|-------|-------|------|------|------|------|------|-------|-------|--|
| 1917-21 | .067 | .127 | .234 | .578 | 1.202 | 2.171 | 2.803 | .067 | .108 | .198 | .354 | .745 | 1.617 | 1.979 |  |
| 1922-26 | .059 | .109 | .301 | .657 | 1.314 | 2.682 | 3.230 | .043 | .108 | .194 | .364 | .920 | 1.940 | 2.532 |  |
| 1927-30 | .062 | .137 | .269 | .550 | 1.163 | 2.239 | 3.240 | .047 | .077 | .175 | .297 | .727 | 1.700 | 2.563 |  |
| 1931-35 | .041 | .089 | .220 | .537 | 1.295 | 2.500 | 3.777 | .026 | .066 | .131 | .283 | .696 | 1.786 | 2.748 |  |
| 1936-40 | .031 | .091 | .229 | .527 | 1.280 | 2.008 | 3.909 | .026 | .058 | .103 | .240 | .605 | 1.602 | 3.097 |  |
| 1941-45 | .025 | .045 | .136 | .294 | .619  | 1.181 | 1.780 | .018 | .031 | .034 | .095 | .238 | .601  | 1.049 |  |
| 1946-50 | .024 | .038 | .110 | .292 | .606  | 1.162 | 1.748 | .015 | .022 | .041 | .072 | .221 | .606  | .792  |  |
| 1951-57 | .015 | .031 | .105 | .284 | .511  | 1.035 | 1.612 | .012 | .012 | .025 | .052 | .168 | .483  | .823  |  |

## 22. Pneumonia

|         |       |       |      |       |       |       |        |      |      |      |      |       |       |        |  |
|---------|-------|-------|------|-------|-------|-------|--------|------|------|------|------|-------|-------|--------|--|
| 1917-21 | 1.156 | 1.026 | .888 | 1.049 | 1.875 | 4.046 | 6.429  | .891 | .729 | .577 | .806 | 1.872 | 3.888 | 6.171  |  |
| 1922-26 | .254  | .315  | .487 | .828  | 1.738 | 4.019 | 6.865  | .157 | .252 | .331 | .632 | 1.523 | 3.925 | 7.103  |  |
| 1927-30 | .233  | .359  | .572 | .835  | 1.848 | 4.631 | 10.467 | .153 | .283 | .378 | .704 | 1.678 | 4.609 | 10.548 |  |
| 1931-35 | .166  | .259  | .463 | .761  | 1.615 | 4.703 | 12.009 | .115 | .208 | .335 | .597 | 1.617 | 5.329 | 12.533 |  |
| 1936-40 | .182  | .239  | .382 | .811  | 1.732 | 5.475 | 17.445 | .106 | .173 | .278 | .605 | 1.735 | 6.148 | 17.840 |  |
| 1941-45 | .121  | .161  | .324 | .626  | 1.483 | 4.546 | 17.079 | .077 | .098 | .159 | .400 | 1.215 | 4.831 | 17.853 |  |
| 1946-50 | .040  | .048  | .125 | .269  | .769  | 3.293 | 15.369 | .029 | .050 | .111 | .204 | .898  | 3.889 | 18.173 |  |
| 1951-57 | .014  | .025  | .050 | .140  | .444  | 1.971 | 11.561 | .015 | .020 | .041 | .084 | .362  | 2.158 | 12.965 |  |

## 23 Bronchitis and asthma

|         |      |      |      |      |      |       |       |      |      |      |      |       |       |       |  |
|---------|------|------|------|------|------|-------|-------|------|------|------|------|-------|-------|-------|--|
| 1917-21 | .031 | .023 | .091 | .295 | .585 | 2.741 | 5.179 | .025 | .033 | .069 | .304 | 1.122 | 3.037 | 5.359 |  |
| 1922-26 | .016 | .026 | .063 | .238 | .751 | 2.468 | 4.644 | .011 | .032 | .073 | .216 | .798  | 2.534 | 4.509 |  |
| 1927-30 | .005 | .015 | .063 | .174 | .523 | 1.875 | 4.003 | .011 | .015 | .029 | .142 | .578  | 2.031 | 4.561 |  |
| 1931-35 | .008 | .015 | .043 | .111 | .361 | 1.462 | 3.743 | .006 | .019 | .032 | .111 | .383  | 1.657 | 3.856 |  |
| 1936-40 | .008 | .010 | .044 | .150 | .333 | 1.082 | 4.085 | .011 | .024 | .034 | .063 | .270  | 1.174 | 3.949 |  |
| 1941-45 | .011 | .019 | .043 | .096 | .220 | .849  | 3.214 | .010 | .015 | .035 | .081 | .243  | .848  | 3.232 |  |
| 1946-50 | .008 | .010 | .042 | .097 | .185 | .603  | 2.507 | .003 | .009 | .029 | .062 | .175  | .572  | 2.450 |  |
| 1951-57 | .004 | .010 | .026 | .131 | .285 | .610  | 2.050 | .003 | .009 | .030 | .070 | .154  | .525  | 1.979 |  |

## 24 Other diseases of respiratory organs

|         |      |      |      |      |      |      |      |      |      |      |      |      |      |      |  |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|--|
| 1917-21 | .094 | .087 | .104 | .171 | .244 | .351 | .264 | .063 | .056 | .063 | .125 | .101 | .221 | .132 |  |
| 1922-26 | .080 | .065 | .099 | .140 | .279 | .349 | .310 | .034 | .044 | .078 | .105 | .165 | .207 | .271 |  |
| 1927-30 | .051 | .047 | .081 | .115 | .245 | .406 | .467 | .031 | .039 | .042 | .073 | .102 | .210 | .312 |  |
| 1931-35 | .056 | .061 | .076 | .135 | .211 | .322 | .379 | .021 | .028 | .041 | .063 | .126 | .220 | .345 |  |
| 1936-40 | .038 | .048 | .071 | .150 | .188 | .336 | .397 | .028 | .030 | .042 | .061 | .066 | .190 | .257 |  |
| 1941-45 | .044 | .045 | .094 | .161 | .277 | .435 | .498 | .024 | .030 | .046 | .048 | .122 | .199 | .371 |  |
| 1946-50 | .012 | .018 | .037 | .073 | .177 | .225 | .401 | .007 | .014 | .021 | .033 | .076 | .156 | .276 |  |
| 1951-57 | .006 | .009 | .034 | .096 | .210 | .369 | .590 | .003 | .005 | .015 | .037 | .098 | .233 | .451 |  |

# APPENDIX IV (cont.)

| MALES |       |       |       |       |       |     |  | FEMALES |       |       |       |       |       |     |  |
|-------|-------|-------|-------|-------|-------|-----|--|---------|-------|-------|-------|-------|-------|-----|--|
| 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ |  | 20-29   | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+ |  |

## 25. Gastro-duodenal ulcer

|         |      |      |      |      |      |      |      |      |      |      |      |      |      |  |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|--|
| 1917-21 | .034 | .057 | .109 | .163 | .241 | .200 | .222 | .033 | .050 | .106 | .142 | .185 | .185 |  |
| 1922-26 | .030 | .083 | .155 | .196 | .282 | .286 | .215 | .021 | .053 | .075 | .117 | .158 | .185 |  |
| 1927-30 | .041 | .102 | .132 | .227 | .277 | .427 | .202 | .011 | .023 | .078 | .123 | .175 | .272 |  |
| 1931-35 | .039 | .078 | .145 | .196 | .281 | .427 | .367 | .007 | .030 | .053 | .095 | .178 | .242 |  |
| 1936-40 | .037 | .094 | .152 | .216 | .317 | .478 | .429 | .005 | .027 | .059 | .092 | .163 | .263 |  |
| 1941-45 | .030 | .091 | .164 | .183 | .279 | .485 | .483 | .004 | .017 | .029 | .074 | .151 | .258 |  |
| 1946-50 | .011 | .042 | .078 | .138 | .207 | .310 | .500 | .001 | .009 | .015 | .026 | .105 | .222 |  |
| 1951-57 | .010 | .023 | .056 | .111 | .163 | .329 | .427 | .001 | .002 | .008 | .024 | .067 | .163 |  |

## 26. Acute and chronic gastric catarrh

|         |      |      |      |      |      |      |       |      |      |      |      |      |      |  |
|---------|------|------|------|------|------|------|-------|------|------|------|------|------|------|--|
| 1917-21 | .025 | .037 | .038 | .097 | .164 | .526 | .542  | .031 | .036 | .068 | .114 | .238 | .485 |  |
| 1922-26 | .015 | .019 | .046 | .102 | .142 | .411 | .498  | .012 | .021 | .044 | .062 | .160 | .389 |  |
| 1927-30 | .010 | .013 | .029 | .064 | .105 | .172 | .411  | .014 | .021 | .029 | .034 | .123 | .247 |  |
| 1931-35 | .016 | .011 | .013 | .032 | .070 | .217 | .344  | .006 | .020 | .028 | .042 | .102 | .207 |  |
| 1936-40 | .010 | .011 | .024 | .048 | .045 | .184 | .568  | .011 | .016 | .023 | .051 | .103 | .217 |  |
| 1941-45 | .018 | .030 | .037 | .061 | .132 | .389 | 1.241 | .013 | .026 | .037 | .057 | .171 | .450 |  |
| 1946-50 | .003 | .006 | .013 | .032 | .042 | .184 | .678  | .006 | .007 | .011 | .018 | .062 | .181 |  |
| 1951-57 | .001 | .005 | .006 | .014 | .027 | .082 | .326  | .002 | .002 | .004 | .008 | .024 | .100 |  |

## 27. Ileus and hernia

|         |      |      |      |      |      |      |       |      |      |      |      |      |      |  |
|---------|------|------|------|------|------|------|-------|------|------|------|------|------|------|--|
| 1917-21 | .021 | .041 | .076 | .165 | .419 | .906 | .972  | .034 | .039 | .079 | .135 | .270 | .559 |  |
| 1922-26 | .021 | .032 | .053 | .132 | .306 | .69  | 1.036 | .018 | .031 | .077 | .112 | .221 | .598 |  |
| 1927-30 | .025 | .024 | .051 | .135 | .258 | .710 | 1.335 | .012 | .030 | .054 | .119 | .227 | .515 |  |
| 1931-35 | .016 | .076 | .055 | .114 | .264 | .649 | 1.217 | .015 | .021 | .072 | .10  | .258 | .549 |  |
| 1936-40 | .01  | .076 | .071 | .110 | .261 | .628 | 1.694 | .01  | .029 | .068 | .16  | .214 | .701 |  |
| 1941-45 | .020 | .026 | .071 | .142 | .371 | .770 | 1.800 | .017 | .017 | .074 | .16  | .361 | .746 |  |
| 1946-50 | .011 | .013 | .033 | .053 | .1   | .403 | 1.204 | .002 | .008 | .022 | .049 | .156 | .478 |  |
| 1951-57 | .007 | .007 | .010 | .017 | .126 | .40  | 1.266 | .003 | .006 | .016 | .027 | .115 | .364 |  |

## 28. Appendicitis

|         |      |      |      |      |      |      |      |      |      |      |      |      |      |  |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|--|
| 1917-21 | .077 | .057 | .048 | .087 | .021 | .073 | .083 | .054 | .072 | .044 | .032 | .066 | .102 |  |
| 1922-26 | .078 | .065 | .072 | .067 | .097 | .103 | .081 | .043 | .049 | .032 | .033 | .012 | .046 |  |
| 1927-30 | .114 | .044 | .079 | .072 | .07  | .078 | .166 | .033 | .042 | .041 | .071 | .076 | .066 |  |
| 1931-35 | .09  | .077 | .091 | .078 | .13  | .073 | .103 | .042 | .038 | .031 | .057 | .069 | .072 |  |
| 1936-40 | .07  | .07  | .081 | .079 | .097 | .111 | .077 | .024 | .030 | .04  | .046 | .064 | .089 |  |
| 1941-45 | .074 | .069 | .05  | .068 | .06  | .089 | .081 | .026 | .025 | .023 | .034 | .035 | .077 |  |
| 1946-50 | .077 | .026 | .031 | .040 | .046 | .116 | .092 | .003 | .013 | .017 | .016 | .031 | .066 |  |
| 1951-57 | .007 | .009 | .015 | .019 | .024 | .054 | .107 | .005 | .003 | .003 | .010 | .021 | .063 |  |

# APPENDIX IV (cont.)

|                       | MALES |       |       |       |       |       |      | FEMALES |       |       |       |       |       |      |
|-----------------------|-------|-------|-------|-------|-------|-------|------|---------|-------|-------|-------|-------|-------|------|
|                       | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+  | 20-29   | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+  |
| 29 Cirrhosis of liver |       |       |       |       |       |       |      |         |       |       |       |       |       |      |
| 1917-21               | .001  | .020  | .036  | .037  | .107  | .083  | .133 | .001    | .007  | .015  | .016  | .032  | .055  | .031 |
| 1922-26               | .003  | .006  | .019  | .026  | .103  | .080  | .054 | .001    | .001  | .015  | .022  | .035  | .068  | .048 |
| 1927-30               | .001  | .012  | .037  | .071  | .118  | .115  | .062 | .001    | .005  | .016  | .024  | .044  | .037  | .045 |
| 1931-35               | .001  | .013  | .026  | .084  | .126  | .077  | .115 | .001    | .003  | .015  | .026  | .022  | .053  | .041 |
| 1936-40               | .002  | .004  | .027  | .068  | .110  | .138  | .139 | .001    | .002  | .007  | .027  | .069  | .056  | .069 |
| 1941-45               | .001  | .006  | .024  | .049  | .056  | .096  | .061 | .001    | .005  | .010  | .029  | .080  | .062  | .064 |
| 1946-50               | .001  | .004  | .018  | .052  | .085  | .128  | .143 | .002    | .003  | .015  | .055  | .084  | .161  | .101 |
| 1951-57               | .004  | .007  | .028  | .070  | .140  | .213  | .169 | .003    | .003  | .018  | .044  | .086  | .184  | .224 |

## 30. Diseases of bile ducts and gall bladder

|         |      |      |      |      |      |      |      |      |      |      |      |      |      |       |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|-------|
| 1917-21 | .003 | .008 | .013 | .027 | .074 | .068 | .139 | .003 | .007 | .021 | .053 | .103 | .183 | .203  |
| 1922-26 | .003 | .001 | .013 | .030 | .074 | .161 | .121 | .003 | .014 | .043 | .035 | .141 | .314 | .242  |
| 1927-30 | .003 | .007 | .022 | .037 | .099 | .167 | .312 | .003 | .014 | .041 | .101 | .175 | .350 | .468  |
| 1931-35 | .002 | .003 | .014 | .034 | .107 | .181 | .402 | .002 | .009 | .040 | .083 | .225 | .393 | .648  |
| 1936-40 | .002 | .003 | .009 | .030 | .110 | .176 | .533 | .002 | .014 | .024 | .075 | .184 | .443 | .742  |
| 1941-45 | .001 | .002 | .009 | .017 | .006 | .200 | .407 | .002 | .008 | .016 | .061 | .116 | .400 | .728  |
| 1946-50 | .001 | .001 | .004 | .035 | .063 | .240 | .397 | .001 | .001 | .015 | .048 | .151 | .427 | .955  |
| 1951-57 | .001 | .001 | .007 | .026 | .079 | .207 | .522 | .001 | .003 | .012 | .033 | .127 | .411 | 1.209 |

## 31 Other diseases of digestive organs

|         |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
|---------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 1917-21 | .068 | .064 | .076 | .203 | .268 | .375 | .361 | .103 | .135 | .119 | .180 | .243 | .366 | .416 |
| 1922-26 | .082 | .075 | .114 | .172 | .316 | .402 | .498 | .096 | .128 | .153 | .143 | .258 | .393 | .339 |
| 1927-30 | .041 | .046 | .083 | .133 | .287 | .307 | .576 | .071 | .103 | .097 | .123 | .183 | .373 | .333 |
| 1931-35 | .031 | .036 | .066 | .102 | .191 | .354 | .436 | .046 | .058 | .079 | .077 | .162 | .264 | .468 |
| 1936-40 | .029 | .032 | .064 | .113 | .222 | .306 | .483 | .037 | .044 | .047 | .080 | .184 | .321 | .532 |
| 1941-45 | .040 | .046 | .108 | .161 | .216 | .424 | .763 | .072 | .067 | .079 | .094 | .154 | .312 | .706 |
| 1946-50 | .015 | .029 | .039 | .070 | .131 | .309 | .624 | .020 | .021 | .043 | .087 | .119 | .248 | .578 |
| 1951-57 | .007 | .010 | .028 | .047 | .083 | .225 | .433 | .009 | .009 | .018 | .039 | .103 | .223 | .468 |

## 32 Nephritis

|         |      |      |      |      |       |       |       |      |      |      |      |      |       |       |
|---------|------|------|------|------|-------|-------|-------|------|------|------|------|------|-------|-------|
| 1917-21 | .190 | .196 | .371 | .777 | 1.172 | 1.42  | 1.527 | .129 | .183 | .329 | .568 | .930 | 1.142 | .995  |
| 1922-26 | .079 | .163 | .336 | .689 | 1.104 | 1.566 | 1.373 | .109 | .197 | .347 | .511 | .818 | 1.069 | .919  |
| 1927-30 | .099 | .196 | .335 | .665 | 1.300 | 1.838 | 2.243 | .098 | .159 | .325 | .326 | .899 | 1.244 | 1.182 |
| 1931-35 | .080 | .162 | .266 | .607 | 1.082 | 2.023 | 2.744 | .071 | .143 | .238 | .401 | .821 | 1.161 | 1.370 |
| 1936-40 | .063 | .120 | .233 | .533 | .916  | 2.015 | 3.517 | .061 | .106 | .213 | .405 | .667 | 1.171 | 1.347 |
| 1941-45 | .064 | .089 | .176 | .293 | .710  | 1.262 | 2.879 | .040 | .064 | .134 | .268 | .472 | .803  | 1.213 |
| 1946-50 | .039 | .066 | .120 | .268 | .521  | 1.012 | 2.834 | .030 | .054 | .099 | .191 | .363 | .718  | 1.081 |
| 1951-57 | .038 | .062 | .092 | .182 | .303  | .483  | .904  | .022 | .045 | .070 | .114 | .207 | .402  | .584  |

# APPENDIX V

Death rates per 1,000 from all causes in Oslo in the various calendar year groups

|         | AGE   |       |        |        |        |        |         |
|---------|-------|-------|--------|--------|--------|--------|---------|
|         | 20-29 | 30-39 | 40-49  | 50-59  | 60-69  | 70-79  | 80 +    |
| MALES   |       |       |        |        |        |        |         |
| 1917-21 | 6.214 | 8.044 | 10.675 | 18.119 | 38.213 | 89.502 | 221.033 |
| 1922-26 | 4.913 | 6.064 | 10.058 | 18.623 | 38.300 | 87.331 | 185.278 |
| 1927-30 | 4.839 | 6.223 | 10.206 | 16.607 | 37.748 | 76.393 | 171.387 |
| 1931-35 | 3.513 | 4.980 | 8.213  | 16.047 | 36.021 | 78.663 | 167.432 |
| 1936-40 | 2.493 | 4.305 | 8.582  | 16.242 | 36.112 | 85.877 | 204.101 |
| 1941-45 | 3.130 | 3.936 | 8.098  | 13.661 | 29.895 | 64.167 | 161.116 |
| 1946-50 | 1.391 | 2.001 | 5.139  | 11.487 | 26.580 | 64.776 | 172.270 |
| 1951-57 | .898  | 1.366 | 3.879  | 11.298 | 27.647 | 65.694 | 159.642 |
| FEMALES |       |       |        |        |        |        |         |
| 1917-21 | 5.880 | 6.467 | 7.701  | 12.699 | 26.801 | 63.570 | 173.269 |
| 1922-26 | 3.702 | 4.100 | 7.098  | 11.863 | 24.493 | 64.202 | 170.569 |
| 1927-30 | 3.704 | 3.974 | 6.070  | 10.940 | 25.584 | 61.588 | 156.159 |
| 1931-35 | 2.555 | 3.154 | 5.120  | 9.923  | 23.031 | 63.182 | 161.836 |
| 1936-40 | 1.780 | 2.800 | 4.713  | 9.754  | 23.511 | 61.888 | 170.034 |
| 1941-45 | 1.824 | 2.328 | 4.094  | 7.173  | 18.997 | 52.090 | 148.779 |
| 1946-50 | .975  | 1.523 | 2.840  | 6.210  | 16.916 | 49.992 | 148.753 |
| 1951-57 | .446  | 1.006 | 2.130  | 5.561  | 14.935 | 45.936 | 139.703 |

Aker included from 1 January 1948.

# APPENDIX VI

Death rates per 1 000 in Oslo in 1931-57 for the cause groups defined in Appendix II

|     |   | AGE   |       |       |       |       |       |        |
|-----|---|-------|-------|-------|-------|-------|-------|--------|
|     |   | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80+    |
| 1   | Tuberculosis of resp. system            |       |       |       |       |       |       |        |
|     | Males                                   | .046  | 134   | 170   | .395  | .583  | .551  | .868   |
|     | Females                                 | .023  | 108   | 078   | .066  | 149   | .218  | 419    |
| 2.  | Other forms of tuberculosis             |       |       |       |       |       |       |        |
|     | Males                                   | .005  | 013   | 013   | .020  | 064   | 103   | .062   |
|     | Females                                 | -     | .007  | .021  | .023  | .036  | .021  | 030    |
| 3.  | Syphilis                                |       |       |       |       |       |       |        |
|     | Males                                   | -     | -     | .022  | 151   | .367  | .569  | .248   |
|     | Females                                 | -     | .004  | .011  | .046  | .072  | 197   | .060   |
| 4   | Influenza                               |       |       |       |       |       |       |        |
|     | Males                                   | -     | -     | .004  | .005  | -     | -     | .248   |
|     | Females                                 | -     | -     | -     | -     | -     | .021  | 150    |
| 5.  | Other infectious and parasitic diseases |       |       |       |       |       |       |        |
|     | Males                                   | .031  | 050   | 035   | .099  | .024  | 121   | .372   |
|     | Females                                 | .036  | .033  | 018   | .027  | .066  | 145   | 479    |
| 6.  | Cancer of oesophagus                    |       |       |       |       |       |       |        |
|     | Males                                   | -     | -     | .022  | 117   | 447   | 1.068 | .992   |
|     | Females                                 | -     | -     | 004   | 008   | .048  | 145   | .330   |
| 7   | Cancer of stomach                       |       |       |       |       |       |       |        |
|     | Males                                   | -     | .025  | 163   | .576  | 1.500 | 3.671 | 6.879  |
|     | Females                                 | -     | .041  | .086  | .267  | .663  | 1.887 | 3.745  |
| 8.  | Other cancers of digestive organs       |       |       |       |       |       |       |        |
|     | Males                                   | .005  | 021   | 117   | .585  | 1.461 | 3.447 | 4.957  |
|     | Females                                 | 009   | .015  | 092   | .298  | .902  | 2.239 | 4.733  |
| 9   | Cancer of pharynx                       |       |       |       |       |       |       |        |
|     | Males                                   | -     | -     | .009  | .039  | 184   | .327  | 496    |
|     | Females                                 | -     | -     | -     | .015  | .042  | .010  | .060   |
| 10. | Cancer of larynx                        |       |       |       |       |       |       |        |
|     | Males                                   | -     | -     | 009   | .015  | .072  | 138   | .372   |
|     | Females                                 | -     | -     | -     | -     | -     | -     | -      |
| 11  | Cancer of lung                          |       |       |       |       |       |       |        |
|     | Males                                   | .010  | .013  | 174   | .805  | .998  | .862  | .558   |
|     | Females                                 | -     | .011  | 018   | 083   | 173   | 166   | .270   |
| 12. | Leukaemia and alukaemia                 |       |       |       |       |       |       |        |
|     | Males                                   | .010  | .025  | 057   | 117   | .303  | 483   | 744    |
|     | Females                                 | 027   | .033  | 043   | 112   | 167   | 197   | .389   |
| 13  | All other malignant tumours             |       |       |       |       |       |       |        |
|     | Males                                   | 118   | 150   | .332  | .814  | 2.242 | 4.756 | 10.535 |
|     | Females                                 | 036   | .241  | .784  | 1.700 | 2.516 | 4.303 | 6.051  |
| 14  | Diabetes mellitus                       |       |       |       |       |       |       |        |
|     | Males                                   | .010  | .025  | .057  | .083  | .239  | .327  | 744    |
|     | Females                                 | .009  | .015  | 018   | .054  | 167   | .342  | .639   |
| 15. | Psychoses                               |       |       |       |       |       |       |        |
|     | Males                                   | -     | .013  | 013   | .020  | .016  | 121   | 186    |
|     | Females                                 | .009  | 004   | .004  | .008  | .042  | 166   | .929   |
| 16. | Chronic alcoholism                      |       |       |       |       |       |       |        |
|     | Males                                   | -     | .008  | .013  | .020  | .016  | .034  | -      |
|     | Females                                 | -     | -     | -     | -     | -     | -     | -      |



# APPENDIX VI (cont.)

|  |         | AGE   |       |       |       |       |        |        |
|--|---------|-------|-------|-------|-------|-------|--------|--------|
|  |         | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79  | 80+    |
| 17 Apoplexy                                      | Males   | .021  | .034  | .192  | .732  | 3 105 | 11.029 | 26.462 |
|  | Females | .014  | .026  | .136  | .507  | 2.379 | 9.351  | 28.073 |
| 18. Coronary heart disease                       | Males   | .021  | .101  | .633  | 2.971 | 7.878 | 17.457 | 36.316 |
|  | Females | -     | .022  | .086  | .472  | 2.773 | 9.818  | 29.121 |
| 19. Valvular heart disease                       | Males   | .005  | .021  | .109  | .190  | .463  | .982   | 1.735  |
|  | Females | .005  | .030  | .082  | .232  | .442  | 1.057  | 3.0.6  |
| 20. Other diseases of cardiovascular system      | Males   | .026  | .059  | .126  | .659  | 2.051 | 6.152  | 17.558 |
|  | Females | .009  | .026  | .111  | .468  | 1.566 | 6.002  | 18.755 |
| 21 Sudden death - heart paralysis                | Males   | .010  | .029  | .122  | .254  | .583  | 1.017  | 1.177  |
|  | Females | .009  | .011  | .018  | .054  | .155  | .559   | .599   |
| 22. Pneumonia                                    | Males   | .026  | .019  | .061  | .220  | .583  | 3.257  | 20.575 |
|  | Females | .005  | -     | .021  | .070  | .317  | 2.820  | 17.377 |
| 23. Bronchitis and asthma                        | Males   | .005  | -     | .026  | .197  | .447  | .534   | 1.177  |
|  | Females | .005  | -     | .021  | .046  | .114  | .301   | 1.228  |
| 24 Other diseases of respiratory organs          | Males   | .005  | -     | .043  | .166  | .519  | .551   | .806   |
|  | Females | -     | .007  | .014  | .050  | .126  | .228   | .599   |
| 25. Gastro-duodenal ulcer                        | Males   | .005  | .038  | .074  | .185  | .303  | .431   | 1.054  |
|  | Females | -     | .004  | .011  | .031  | .090  | .218   | .500   |
| 26. Acute and chronic gastric cancer             | Males   | -     | -     | .004  | .005  | .024  | .103   | .062   |
|  | Females | .005  | .004  | .004  | .008  | .006  | .083   | .360   |
| 27. Pleus and hernia                             | Males   | .003  | -     | .004  | .034  | .120  | .465   | .930   |
|  | Females | -     | .004  | .004  | .031  | .102  | .332   | .929   |
| 28. Appendicitis                                 | Males   | .015  | .013  | .017  | .020  | .008  | .069   | .124   |
|  | Females | .003  | .004  | -     | .004  | .018  | .093   | .180   |
| 29. Cirrhosis of liver                           | Males   | .005  | .029  | .061  | .195  | .383  | .707   | .682   |
|  | Females | .005  | -     | .025  | .093  | .227  | .456   | .539   |
| 30. Diseases of bile ducts and gall bladder      | Males   | -     | -     | .004  | .068  | .120  | .310   | 1.054  |
|  | Females | -     | .007  | .014  | .019  | .131  | .363   | 2.037  |
| 31 Other diseases of digestive organs            | Males   | -     | .008  | .035  | .078  | .128  | .293   | .434   |
|  | Females | .014  | .004  | .025  | .058  | .108  | .238   | .899   |
| 32. Nephritis                                    | Males   | .046  | .063  | .131  | .127  | .319  | .396   | .744   |
|  | Females | .023  | .048  | .064  | .104  | .173  | .321   | .659   |
| 33. Other diseases of urinary and genital organs | Males   | .005  | .008  | .017  | .034  | .375  | 2.120  | 7.747  |
|  | Females | -     | .011  | .036  | .035  | .114  | .446   | 1.138  |

## APPENDIX VI (cont.)

|            |  | AGE   |       |       |        |        |        |         |
|------------|--|-------|-------|-------|--------|--------|--------|---------|
|            |  | 20-29 | 30-39 | 40-49 | 50-59  | 60-69  | 70-79  | 80+     |
| 34         | Complications of pregnancy, childbirth, and puerperium           |       |       |       |        |        |        |         |
|            | Females  | .011  | .059  | .007  | -      | -      | -      | -       |
| 35         | Diseases of skin, cellular tissue, bones, and organs of movement |       |       |       |        |        |        |         |
|            | Males  | -     | -     | .076  | .015   | .064   | .103   | .434    |
|            | Females  | -     | .007  | .007  | .031   | .060   | .207   | .719    |
| 36         | Senility   |       |       |       |        |        |        |         |
|            | Males  | -     | -     | -     | -      | -      | .155   | 2.107   |
|            | Females  | -     | -     | -     | -      | -      | .207   | 4.164   |
| 37         | Selficide  |       |       |       |        |        |        |         |
|            | Males  | .092  | .168  | .253  | .307   | .311   | .190   | .124    |
|            | Females  | .036  | .037  | .080  | .128   | .084   | .052   | .090    |
| 38         | Accidents and homicide   |       |       |       |        |        |        |         |
|            | Males  | .293  | .385  | .470  | .586   | .790   | 1.378  | 6.321   |
|            | Females  | .068  | .074  | .063  | .127   | .334   | 1.316  | 7.130   |
| 39         | Other and unknown causes   |       |       |       |        |        |        |         |
|            | Males  | .077  | .121  | .218  | .517   | .758   | 1.415  | 3.780   |
|            | Females  | .059  | .108  | .146  | .283   | .574   | 1.410  | 3.266   |
| All causes |  |       |       |       |        |        |        |         |
|            | Males  | .898  | 1.566 | 3.879 | 11.298 | 27.647 | 65.694 | 159.642 |
|            | Females  | .446  | 1.006 | 2.150 | 5.561  | 14.935 | 45.936 | 159.703 |

## APPENDIX VII

Death rates per 1,000 in Oslo\* in 1941-45 and 1946-50 for 13 cause groups

|                              | M A L E S          |                |              |              |              |                |                |                |            |            | F E M A L E S |                |                |                |            |            |                |                |                |  |
|------------------------------|--------------------|----------------|--------------|--------------|--------------|----------------|----------------|----------------|------------|------------|---------------|----------------|----------------|----------------|------------|------------|----------------|----------------|----------------|--|
|                              | 1941-45<br>1946-50 | 20-29<br>30-39 | 40-49        | 50-59        | 60-69        | 70-79          | 80 +           | 20-29<br>30-39 | 40-49      | 50-59      | 60-69         | 70-79          | 80 +           | 20-29<br>30-39 | 40-49      | 50-59      | 60-69          | 70-79          | 80 +           |  |
| Tuberculosis of resp. syst., | 1941-45<br>1946-50 | 659<br>297     | 910<br>484   | 1,210<br>735 | 1,267<br>956 | 1,261<br>882   | 1,949<br>707   | 1,204<br>1,345 | 400<br>246 | 233<br>221 | 409<br>289    | 290<br>465     | 748<br>502     | 391<br>354     | 400<br>246 | 233<br>221 | 409<br>289     | 290<br>465     | 748<br>502     |  |
| Other forms of tuberculosis  | 1941-45<br>1946-50 | 124<br>013     | 120<br>020   | 047<br>049   | 055<br>044   | 067<br>050     | 185            | -              | 079<br>042 | 069<br>033 | 059<br>018    | 083<br>056     | 063<br>056     | 069<br>054     | 069<br>033 | 059<br>035 | -              | 018            | 056            |  |
| Cancer of oesophagus         | 1941-45<br>1946-50 | -              | -            | 056<br>028   | 317<br>167   | 752<br>689     | 1,438<br>1,229 | 602<br>1,100   | -          | 022<br>006 | 011<br>014    | 068<br>185     | 249<br>335     | -              | 022<br>006 | 011<br>014 | 068<br>185     | 249<br>335     | 249<br>335     |  |
| Cancer of stomach            | 1941-45<br>1946-50 | 009<br>003     | 034<br>003   | 298<br>208   | 716<br>772   | 2,235<br>1,715 | 4,083<br>3,841 | 5,417<br>6,847 | 007<br>-   | 082<br>035 | 1315<br>406   | 5,063<br>2,281 | 4,901<br>4,797 | 082<br>035     | 222<br>134 | 494<br>406 | 1,315<br>849   | 5,063<br>2,281 | 4,901<br>4,797 |  |
| Cancer of pharynx            | 1941-45<br>1946-50 | -              | 009<br>-     | 028<br>014   | 067<br>026   | 155<br>080     | 232<br>032     | 567            | -          | -          | 011           | -              | 056            | -              | -          | -          | -              | 019            | 056            |  |
| Cancer of larynx             | 1941-45<br>1946-50 | -              | -            | 028<br>021   | 078<br>035   | 111<br>096     | 093<br>246     | 201            | -          | -          | -             | -              | -              | -              | 006        | -          | 022            | -              | -              |  |
| Cancer of lung               | 1941-45<br>1946-50 | -              | 009<br>020   | 168<br>104   | 248<br>335   | 420<br>345     | 371<br>615     | 602            | -          | -          | 106           | 117            | 166            | -              | 052        | 106        | 117            | 264            | 166            |  |
| Leukaemia                    | 1941-45<br>1946-50 | 018<br>014     | 009<br>015   | 037<br>055   | 065<br>070   | 177<br>144     | 278<br>615     | 613            | 007<br>006 | 014<br>011 | 032<br>122    | 079<br>242     | 166            | 007<br>006     | 044<br>006 | 032<br>037 | 132<br>122     | 079<br>242     | 166            |  |
| Pneumonia                    | 1941-45<br>1946-50 | 106<br>051     | 137<br>053   | 642<br>236   | 1,184<br>605 | 2,943<br>1,828 | 9,372<br>9,649 | 32,303         | 066<br>036 | 069<br>006 | 163<br>385    | 1,944<br>8,409 | 31,890         | 066<br>006     | 163<br>145 | 466<br>385 | 1,944<br>8,409 | 31,890         | 31,890         |  |
| Carbuncles of liver          | 1941-45<br>1946-50 | -              | -            | 074<br>065   | 065<br>114   | 133<br>206     | 418<br>399     | 967            | -          | -          | 022<br>056    | 238<br>279     | 249            | -              | 022<br>056 | 011<br>100 | 292<br>223     | 238<br>279     | 249            |  |
| Scarlait                     | 1941-45<br>1946-50 | -              | 009          | -            | 041          | 133            | 1,299          | 14,446         | -          | -          | 007           | 161            | 14,451         | -              | 007        | 045        | 115            | 14,507         | 14,507         |  |
| Subsidiary                   | 1941-45<br>1946-50 | 044<br>167     | 120<br>199   | 177<br>340   | 262<br>342   | 221<br>417     | 139<br>184     | 201            | 043<br>036 | 055<br>061 | 052<br>100    | 079<br>122     | 079            | 043<br>061     | 052<br>100 | 052<br>100 | 079<br>122     | 079            | -              |  |
| Accidents and homicide       | 1941-45<br>1946-50 | 1,082<br>582   | 1,193<br>571 | 1,966<br>617 | 1,749<br>666 | 728<br>912     | 2,320<br>1,444 | 6,822          | 260<br>061 | 251<br>094 | 371           | 498            | 10,301         | 260<br>061     | 251<br>094 | 371        | 498            | 2,508          | 10,301         |  |

After included from 1 January 1946.

# APPENDIX VIII

Confidence limits for the expectation of a Poisson variable

| Number of observed<br>events<br>(Actual deaths) | 99 % limits |       | 95 % limits |       | 90 % limits |       |
|---|-------------|-------|-------------|-------|-------------|-------|
|   | Lower       | Upper | Lower       | Upper | Lower       | Upper |
| 0   | .0          | 5.3   | .0          | 3.7   | .0          | 3.0   |
| 1   | .0          | 7.4   | .0          | 5.6   | .1          | 4.7   |
| 2   | 1           | 9.3   | .2          | 7.2   | .4          | 6.3   |
| 3   | 3           | 11.0  | .6          | 8.8   | .8          | 7.8   |
| 4   | 7           | 12.6  | 1.1         | 10.2  | 1.4         | 9.2   |
| 5   | 11          | 14.2  | 1.6         | 11.7  | 2.0         | 10.5  |
| 6   | 15          | 15.7  | 2.2         | 13.1  | 2.6         | 11.8  |
| 7   | 2.0         | 17.1  | 2.8         | 14.4  | 3.3         | 13.2  |
| 8   | 2.6         | 18.6  | 3.5         | 15.8  | 4.0         | 14.4  |
| 9   | 3.1         | 20.0  | 4.1         | 17.1  | 4.7         | 15.7  |
| 10  | 3.7         | 21.4  | 4.8         | 18.4  | 5.4         | 17.0  |
| 11  | 4.3         | 22.8  | 5.5         | 19.7  | 6.2         | 18.2  |
| 12  | 4.9         | 24.1  | 6.2         | 21.0  | 6.9         | 19.4  |
| 13  | 5.6         | 25.5  | 6.9         | 22.2  | 7.7         | 20.7  |
| 14  | 6.2         | 26.8  | 7.7         | 23.5  | 8.5         | 21.9  |
| 15  | 6.9         | 28.2  | 8.4         | 24.7  | 9.3         | 23.1  |
| 16  | 7.6         | 29.5  | 9.2         | 26.0  | 10.0        | 24.3  |
| 17  | 8.3         | 30.8  | 9.9         | 27.2  | 10.8        | 25.5  |
| 18  | 8.9         | 32.1  | 10.7        | 28.5  | 11.6        | 26.7  |
| 19  | 9.6         | 33.4  | 11.4        | 29.7  | 12.4        | 27.9  |
| 20  | 10.4        | 34.7  | 12.2        | 30.9  | 13.3        | 29.1  |
| 21  | 11.1        | 36.0  | 13.0        | 32.1  | 14.1        | 30.2  |
| 22  | 11.8        | 37.2  | 13.8        | 33.3  | 14.9        | 31.4  |
| 23  | 12.5        | 38.5  | 14.6        | 34.5  | 15.7        | 32.6  |
| 24  | 13.3        | 39.7  | 15.4        | 35.7  | 16.6        | 33.8  |
| 25  | 14.0        | 41.0  | 16.2        | 36.9  | 17.4        | 34.9  |
| 26  | 14.7        | 42.3  | 17.0        | 38.1  | 18.2        | 36.1  |
| 27  | 15.5        | 43.5  | 17.8        | 39.3  | 19.1        | 37.2  |
| 28  | 16.2        | 44.7  | 18.6        | 40.5  | 19.9        | 38.4  |
| 29  | 17.0        | 46.0  | 19.4        | 41.7  | 20.8        | 39.5  |
| 30  | 17.8        | 47.2  | 20.2        | 42.8  | 21.6        | 40.7  |
| 35  | 21.6        | 53.3  | 24.4        | 48.7  | 23.9        | 46.4  |
| 40  | 25.6        | 59.4  | 28.6        | 54.5  | 30.2        | 52.1  |
| 45  | 29.6        | 65.3  | 32.8        | 60.2  | 34.6        | 57.7  |
| 50  | 33.7        | 71.3  | 37.1        | 65.9  | 39.0        | 63.3  |
| 60  | 41.9        | 83.0  | 45.8        | 77.2  | 47.9        | 74.4  |
| 70  | 50.3        | 94.6  | 54.6        | 88.4  | 56.8        | 85.4  |
| 80  | 58.8        | 106.1 | 63.4        | 99.6  | 65.9        | 96.3  |
| 90  | 67.4        | 117.5 | 72.4        | 110.6 | 75.0        | 107.2 |
| 100   | 76.1        | 128.8 | 81.4        | 121.6 | 84.1        | 118.1 |



# *Addendum*

A METHOD OF COMPUTING THE EXPOSED-TO-RISK  
BY MEANS OF A PUNCHED CARD SYSTEM

BY JAN RIIS, ACTUARY



### *Introduction*

When our office was requested to perform the machine treatment concerning this investigation the material had in advance been transformed to punched cards and the type of mortality rate been decided.

The method of computing the exposed-to-risk used in this investigation differs from the conventional one. Let it be emphasized at once that the method is quite laborious — it requires for instance a good deal of gang punching — and it may not be preferable unless, as in this case, the groups into which the material is to be divided are numerous and the material itself is comparatively small.

The procedure developed in the following aims at the application of conventional punched card machines (accounting machine, reproducing machine, sorting machine etc.) the processing being different, of course, if, say, an electronic computer is available.

### *The mortality rate*

As measure of the mortality was chosen the central rate, the time of observation (exposed to-risk) defined as follows:

The persons are traced from the date of discharge until their death or if alive, till the anniversary of discharge in 1957 the year of observation thus extending from one anniversary to the next. On the assumption that the deaths are uniformly spread over the year they are all (except death during first stay) considered to occur in the middle of the year of observation. Deaths occurring prior to (or after) the anniversary are considered to leave the observation half a year prior to (or after) the anniversary in the calendar year of death. Like wise, we assume the operations to have taken place in the middle of the year of observation (while lost from observation is considered to occur at the anniversary of discharge in the calendar year of the last information). Finally the date of discharge is located to the middle of the calendar year in which it occurs.

### *Fixing the limits of the observation periods and computing the total number of years of observation*

In order to simplify the machinal treatment, we found it convenient to record on the punched cards the exact date — according to the definitions given above — of the limits of the periods into which the observation is divided,



i.e. the observation period prior to or after the operation. (For unoperated patients the second period equals zero and for patients operated during their first stay the first period equals zero)

Among the other data the punched cards contained in advance

|                                |  |   |
|--------------------------------|--|---|
| The calendar year of discharge |  | U |
| —*— death                      | (or lost from observation)                         | D |
| —*— operation                  | (or if unoperated, death or lost from observation) | O |

and it was also recorded if the death (or operation) did occur prior to or after the anniversary of discharge.

Assuming that D represents the middle of the calendar year (i.e. June 30) and consequently  $D + \frac{1}{2}$  the end of the year (i.e. December 31) the termination date, D of the period after the operation will be as follows, according to the given definitions

|  |                         |
|--|-------------------------|
| By death prior to anniversary of discharge | $D = D - \frac{1}{2}^*$ |
| —*— after —*—                              | $D = D + \frac{1}{2}$   |
| Alive at the end of the investigation      | $D = 1957$              |
| Lost from observation                      | $D = D$                 |
| By death during first stay                 | $D = D$                 |

The value of D was gang punched into the cards and similarly the value of O i.e. the termination date of the period prior to the operation.

This procedure enables us to compute the number of observation years in either of the two periods by simple subtraction

|  |          |
|--|----------|
| Number of observation years prior to operation | $O - U$  |
| —*— after *                                    | $D - O$  |
|  | <hr/>    |
|  | $D' - U$ |

Total number of observation years

By summing up the values U O and D and performing the subtractions mentioned above we obtain the number of observation years for the whole material, thus providing a valuable total check, when dividing the material into subgroups.

### *Introduction of auxiliary values a b c d a' b' c' d'*

While the total number of observation years is easily obtained, difficulties soon arise when the distribution of the exposed to-risk on the desired subgroups is to be performed.

The material had to be divided into a large number of groups, according to these characteristics

The adjusted year of death, D' is used only in determining the years of observation (exposed-to-risk) In the numerator of the mortality rate the deaths always relate to the actual year of death, D

- 1) Age 10-year groups
- 2) a. Prior to operation    Duration since discharge
  - 0- 4 years
  - 5-14    "
  - 15-    "
- b. After operation      Duration since operation
  - 0- 4 years
  - 5-14    "
  - 15-    "
- 3) Calendar year periods 1917-21 1922-26, 1927-30 1931-35  
    1936-40 1941-45 1946-50 and 1951-57

Furthermore the material was to be divided according to different personal characteristics such as sex, location of ulcer and type of operation.

It is obvious that, owing to the limited storage and selector devices of the conventional punched card machines the procedure of performing the distribution of the exposed to-risk will require several operation steps. The attempt to minimize the number of steps and make the procedures convenient to machinal operation led us to the method applied.

The first step in simplifying the problem was to transform the groupings items 1)-3) above into quinquennial groups, whereby the desired groupings items 1) and 2) may be provided by simple summing up from the quinquennial groups. Item 3) the calendar year periods were temporarily transformed into pure quinquennial groups (1916)-20 1921-25 1926-30 1931-35 1936-40 (1960) allowance being made later on for the calendar years 1921 and 1926 which have been placed in wrong periods. The next step is to introduce the 8 auxiliary values a, b c, d, and a b c d which are to be punched into the cards. The meaning of the values is illustrated in the graphical presentation shown below (Fig. 1)

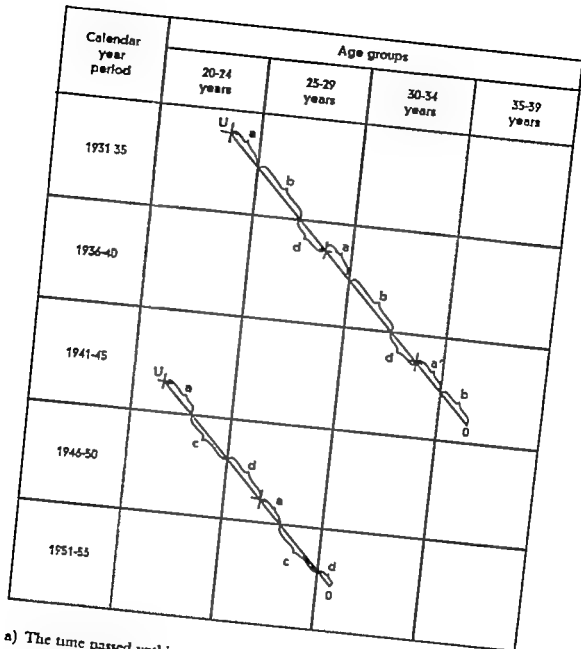
In the Figure are given two examples of the observation period prior to the operation (the procedure being quite similar with respect to the observation period after the operation). The diagonals represent the two lives traced from the date of discharge (L) till the date of operation (O)

As will be seen, the 5th anniversary since discharge is represented by a point on the diagonal (marked by x) in the subsequent square (below to the right). Within this square the 5th anniversary has the same location as has the discharge itself within the preceding square. By thus tracing the life during these 5 years we have passed from one quinquennial age group to another and from one calendar year group to another.

The auxiliary values a, b c, d represent the following fractions of the first 5 years of the observation

The method of adjustment is quite simple and will not be described in this paper

Fig 1



- a) The time passed within the same age group and the same calendar year group as when discharged.
- b) The time passed within the subsequent age group, but in the same calendar year group as when discharged.

- c) The time passed within the same age group as when discharged, but in the subsequent calendar year group
- d) The time passed within the subsequent age group and the subsequent calendar year group, b and c are mutually exclusive therefore one of them will always be equal to zero.

Proceeding from the 5th to the 10th anniversary from the 10th to the 15th anniversary and so forth, and defining a, b, c, d in a similar way the values will obviously remain unchanged, provided the termination of the observation (the operation) does not occur during the period. In the period in which the operation takes place (i.e. the period which involves O) one or more of the values a, b, c, d will be reduced or will be equal to zero. We symbolize the values in this period by a, b, c, d.

*Calculation of exposed-to-risk within one particular (quinquennial) group of age, calendar year and duration since discharge (or operation)*

In the following is described how by means of the auxiliary values, we may calculate the exposed-to-risk in the groups mentioned in the heading. For convenience we concentrate on the period prior to the operation, the method being similar for the period after the operation.

We make use of these symbols (all the groups are assumed to be quinquennial)

$x(t)$  = group of attained age in calendar year group t

p = calendar year group at discharge (involving U)

—•— preceding that in which the operation occurred (i.e. preceding the group involving O)

(x, p and g are numbered as shown in appendix)

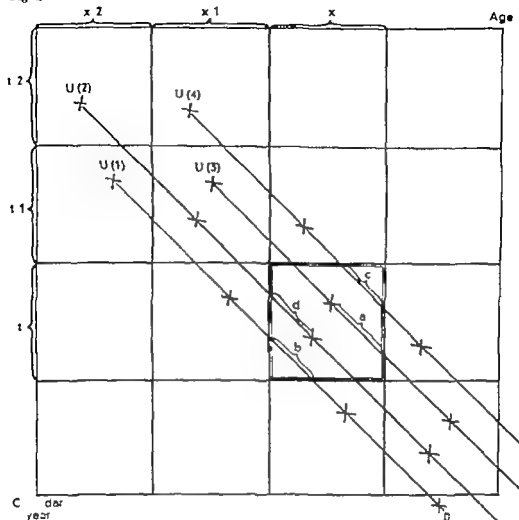
f = group of duration since the discharge (f = 1 in the 1st quinquennial group, f = 2 in the next and so forth)

Fig. 2 expresses in graphical form the life lines of 4 persons, each of them contributing to the exposed-to-risk in a particular combination of the groups (x, t) represented by the marked square. The duration since discharge, f depends upon the location of U (year of discharge) in relation to the marked square.

In Fig. 2 we have chosen f = 2 (i.e. 2nd quinquennial period since discharge). It will be seen that the contribution to exposed-to-risk in the (x, t, f)-group is limited to those discharged in

- |     |                 |         |             |           |            |   |
|-----|-----------------|---------|-------------|-----------|------------|---|
| (1) | calendar year p | = t-f+1 | at age x(p) | = x(t)-f  | b          |   |
| (2) | —•—             | p       | = t-f       | < < < < < | d          |   |
| (3) | —•—             | p       | = t-f+1     | < < x(p)  | = x(t)-f+1 | a |
| (4) | —•—             | p       | = t-f       | < < < < < | c          |   |

Fig 2



It is of course a condition that the observation has not terminated at an earlier point of time, i.e. we disregard cases, where  $g < p + f - 1$ . If  $g = p + f - 1$  (i.e. the operation has taken place in the chosen duration group  $f$ ) the quinquennial duration period is incomplete and the  $a$ ,  $b$ ,  $c$ , and  $d$  are to be substituted by  $a$ ,  $b$ ,  $c$ , and  $d$  respectively.

We will now introduce the value of  $x(o) = x(p) - p$  (cf. Appendix) which, when punched in the cards makes it easy to select the appropriate age groups for a given  $(x, t, f)$ -group.

The desired values of  $x(o)$  and  $g$  will be independent of  $f$ , which will be seen by eliminating  $p$  in the expressions

$x(o) = x(p) - p$  and  $g \leq p + f - 1$  (by means of the conditions made in the survey (1)-(4))

We can now express the contribution to exposed to-risk in the  $(x, t, f)$ -group as shown in Fig. 3

Fig. 3.

|                 |  |                       |                       |
|-----------------|--|-----------------------|-----------------------|
| $p = t - f + 1$ | $\begin{matrix} g > t \\ g = t \end{matrix}$         | $x(o) = x(t) - t$     | $x(t) = x(t) - t + 1$ |
|                 |  | a                     | b                     |
| $p = t - f$     | $\begin{matrix} g > t + 1 \\ g = t + 1 \end{matrix}$ | $x(o) = x(t) - t + 1$ | $x(t) = x(t) - t$     |
|                 |  | c                     | d                     |

To sum up

Given a certain group of calendar year  $t$ , attained age  $x(t)$  and duration since discharge  $f$ . In order to find the exposed-to-risk within this group we have to select the persons (cards) with characteristics  $p, g$  and  $x(o)$  according to the scheme in Fig. 3 and to sum up  $a, b$  etc. according to this scheme.

The card preparations and machine processing will in short be as follows

$p, g, x(p)$  and  $x(o)$  and the auxiliary values  $a, b, c, d$  are gang punched into the cards; the latter by means of mastercards (cf. Appendix). We now duplicate the file making the following adjustments in the new set

The values of  $x(o)$  are lowered by 1 (one unit) while  $p$  and  $g$  are increased by 1. At the same time  $c, d, c$  and  $d$  are placed in the same respective columns in the new set as  $a, b, a$  and  $b$  in the original set (while  $a, b, a$  and  $b$  are dropped in the new set).

By using both sets as one file we can obviously disregard the lower part of Fig. 3 and follow the prescriptions in the upper part solely.

For each value of  $t$  and  $f$  we select (by sorting) the cards with

$g \geq t$  and  $p = t - f + 1$

(or if desired cards with different values of  $p$  corresponding to those values of  $f$  we want to combine). The cards thus selected are then sorted on  $x(o)$  whereafter the accounting machine — for each value of  $x(o)$  — is performing totals  $\Sigma a$  and  $\Sigma b$  choosing  $a$  and  $b$  instead of  $a$  and  $b$  for cards with  $g$  corresponding to the chosen value of  $t$ .

The exposed-to-risk for the different values of  $x(t)$  is finally obtained by adding  $a$  for the appropriate value of  $x(o)$  and  $b$  for the preceding value. This addition was performed by means of desk machines.

# APPENDIX

Code records and master cards

1) x, p, g were coded according to this scheme

| Age group | x  |
|-----------|----|
| 0-4 years | 11 |
| 5-9 "     | 12 |
| 10-14 "   | 13 |
| 15-19 "   | 14 |
| 20-24 "   | 15 |
| 25-29 "   | 16 |
| 30-34 "   | 17 |
| 35-39 "   | 18 |
| 40-44 "   | 19 |
| 45-49 "   | 20 |
| 50-54 "   | 21 |
| 55-59 "   | 22 |
| 60-64 "   | 23 |
| 65-69 "   | 24 |
| 70-74 "   | 25 |
| 75-79 "   | 26 |
| 80-84 "   | 27 |
| 85-89 "   | 28 |
| 90-94 "   | 29 |
| 95-99 "   | 30 |

| Calendar year group | p, g |
|---------------------|------|
| 1917-20             | 1    |
| 1921-25             | 2    |
| 1926-30             | 3    |
| 1931-35             | 4    |
| 1936-40             | 5    |
| 1941-45             | 6    |
| 1946-50             | 7    |
| 1951-55             | 8    |
| 1956-57             | 9    |

The age is determined as follows

Age at discharge U-B  
 " " operation O-B

where { U = calendar year of discharge  
 " = " of birth  
 O = adjusted year of operation

Code number 11 for the lowest age group was chosen (instead of 1) to avoid negative values of  $x(o) = x-p$

2) The gang punching of the auxiliary values a, b, c, d is performed by means of master cards. The preparation of the master cards is comparatively easily done, owing to the fact that there are a limited number of combinations of age at discharge (U-B) calendar year of discharge (U) and year of operation (O) which give different values of a, b, c, d. There are just 25 different sets of values of a, b, c, and d, and 250 different sets of values of a, b, c, and d. Below are given a few examples of such sets.

| Age (U-B)                      | U      | O          | Auxiliary values |     |     |     |     |     |     |     |
|--------------------------------|--------|------------|------------------|-----|-----|-----|-----|-----|-----|-----|
| Last figure + possible decimal |        |            | a                | b   | c   | d   | a   | b   | c   | d   |
| 0 or 5                         | 3 or 8 | 2.0 or 7.0 | 2.5              | -   | 2.5 | -   | 2.5 | -   | 1.5 | -   |
| 1                              |        |            | 2.5              | -   | 1.5 | 1.0 | 2.5 | -   | 1.5 | -   |
| 2                              |        |            | 2.5              | -   | 0.5 | 2.0 | 2.5 | -   | 0.5 | 1.0 |
| 3                              |        |            | 2.0              | 0.5 | -   | 2.5 | 2.0 | 0.5 | -   | 1.5 |
| 4                              |        |            | 1.0              | 1.5 | -   | 2.5 | 1.0 | 1.5 | -   | 1.5 |







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SUPPLEMENTUM 403

A SYSTEM OF  
MICROLITER METHODS SUITABLE FOR  
ROUTINE CLINICAL WORK

BY  
BERTIL THALME

*Accompanies Vol. 174*

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## A System of Microliter<sup>1</sup> Methods Suitable for Routine Clinical Work

By BERTIL THALME

Analytical work on microliter scale was already performed in the thirties by Linderström-Lang and his co-workers in their enzymatic studies [17]. They also devised and constructed several instruments and apparatuses for microliter work.

In recent years several authors have reviewed the development of microliter analysis (Caraway and Fanger [4] Kaplan and del Carmen [15] Kaighis, MacDonald and Ploompau [16] Nateson [21-22] O'Brien, Jibbot and Pinfield [26-27] Sanz [31-32] Seligson [31] Wilkinson [43]).

In 1957 Sanz [32] presented a new equipment for determinations on microliter scale and recently similar equipment constructed by Beckman/Spinco has become commercially available.

The aim of the present investigation has been to determine the accuracy of this equipment and of the Eppendorf flame photometer adapted for microliter analysis.

The Beckman/Spinco Ultramicro Analytical System includes at present equipment and material for 11 clinical chemical tests namely: method for analysis of albumin, bilirubin, calcium, chloride, total cholesterol, creatinine, glucose, inorganic phosphorus, total protein, urea nitrogen and uric acid.

The uric acid analysis method was not tested in this investigation.

Methods for alkaline phosphatase, bicarbonate and urea nitrogen were developed, whereas sodium and potassium were determined flame photometrically on microliter volumes. Some of the chemical methods had to be slightly modified in order to give accurate results, when compared with analytical routine methods hitherto used.

### Equipment

Beckman/Spinco's Ultramicro Analytical System.

This equipment consists of micropipettes, spectrocolorimeter, microtitrator, microcentrifuge and micromixer. Titrations

<sup>1</sup> Microliter (μl) = 1/1000 ml, microliter methods using less than 100 μl.

tion cups made of non fluorescent polyethylene and test tubes made of polyethylene or polypropylene are used.

The Eppendorf flame photometer is adapted for microliter measurements of potassium and sodium [15].

Readings of potassium and sodium require 1.25 ml of solution. The dilution for the determination of potassium and sodium are 1:100 and 1:200 respectively. With a maximum dilution of 1:100-1:200 and a minimum solution volume of 2 ml it is possible to determine potassium and sodium on 20-10  $\mu$ l quantities of plasma. The photomultiplier can be preset on the most suitable sensitivity for the substance analyzed.

### Drawing the sample

Capillary blood was obtained as described by Pincus *et al.* [29]. The first drop of blood was gently wiped away and the second drop of blood was shaken down to the bottom of the test tube with a flick of the wrist and the blood was then allowed to run freely into the 400  $\mu$ l test tube.

### Methods

Microliter methods for determination of bicarbonate, bilirubin, calcium chloride, cholesterol, creatinine, glucose, alkaline phosphatase, inorganic phosphorus, potassium, total protein, sodium and urea nitrogen were studied.

All analyses were made on the Beckman/Spinco Ultramicro Analytical System Model 150 except for the determinations of potassium and sodium which

were analyzed on an Eppendorf flame photometer.

The microliter methods for the analysis of calcium chloride, creatinine and inorganic phosphorus were used as presented in the Instruction Manual for the Beckman/Spinco Ultramicro Analytical System. The methods for determination of bilirubin, cholesterol and total protein were modified and the modifications are discussed in the text. Sodium and potassium were determined on a flame photometer [15]. Analytical routine methods for determination of bicarbonate and alkaline phosphatase were adapted for microliter quantities. Urea nitrogen was determined with the described diacetyl method [8, 10] and with a urease method [41].

The micropipettes used for all of the above-mentioned determinations with exception of glucose had squarely cut ends. For glucose determination, a new type of pipette with drawn-out end was used.

The following two investigations were carried out on blood from newborn infants.

In order to check the precision of the microliter analysis, a large number of analytical determinations were performed on the same sample of plasma.

In addition a significant number of duplicate determinations were carried out, using capillary blood samples.

Because macro methods cannot be used in duplicate determinations on newborn infants capillary blood determinations by analytical routine methods and microliter methods were *not* carried out on the same samples. However comparison of the same type of analysis

by microliter method and routine analytical method was carried out by trained analysts.

The discussed microliter methods were tested against seven macro and six micro methods.<sup>1</sup> For the determination of bicarbonate calcium creatinine glucose, potassium, sodium and urea nitrogen macro methods were used whereas for the determination of bilirubin chloride cholesterol alkaline phosphatase, inorganic phosphorus and total protein micro methods were used.

Preliminary studies of this investigation have shown good agreement between the microliter and routine methods. No statistical data are given as the number of samples analyzed was too small for satisfactory statistic treatment.

### Bicarbonate

A microliter adaptation of the method for titrating the bicarbonate content described by van Slyke *et al* [41] as modified by Johansson [12] is used.

### Reagents

- HCl 0.01 N
- NaCl 0.9% (CO<sub>2</sub>-free)
- NaOH 0.01 N (CO<sub>2</sub>-free)
- Octyl alcohol
- Liquid paraffin
- Phenol red 0.03%
- Bicarbonate standard, NaHCO<sub>3</sub> 0.1 N
- Working bicarbonate standard, NaHCO<sub>3</sub> 0.050 N

### Procedure

Add 20  $\mu$ l plasma and 100  $\mu$ l 0.01 N HCl to a 400  $\mu$ l test tube. Cap the test

tube and mix for 3 minutes in the micromixer. Uncap the test tube and add 5  $\mu$ l octanol. 100  $\mu$ l 0.9% NaCl and 10  $\mu$ l phenol red is then added. Cap the test tube once more and mix for 1 minute in the micromixer. Centrifuge 30 seconds and transfer a 100  $\mu$ l aliquot to a titration cup. Start titration with 0.01 N NaOH.

### Standard

Substitute 90  $\mu$ l of working bicarbonate standard for plasma.

### Solution for comparison

Mix 10  $\mu$ l phenol red in 300  $\mu$ l 0.9% NaCl. Transfer 100  $\mu$ l aliquots of this solution to two titration cups. Add 10  $\mu$ l liquid paraffin to each cup. Finally add 10  $\mu$ l of standard to one cup and 10  $\mu$ l of plasma to the other cup.

Fresh solutions are used and control titration of the NaOH against HCl is performed before the titration of plasma.

The sample and the standard is titrated to the same red color as the color for the plasma and standard in the comparison solution.

### Calculation

50 = amount of used 0.01 N NaOH in  $\mu$ l = mEq NaHCO<sub>3</sub>/L

### Comments

In order to remove the carbon dioxide set free by acid the tube is shaken vigorously in the micromixer for 3 minutes. The shaking gives a foam of bubbles on the surface of the solution. By addition of octyl alcohol the surface tension is reduced and the CO<sub>2</sub> bubbles vanish.

The micro pipettes used have plastic

<sup>1</sup>Macro methods = methods using 1 ml or more; micro methods = methods using 0.1-1.0 ml.

containers with soda lime fitted to exclude introduction of atmospheric  $\text{CO}_2$ .

The standard and plasma are titrated to an endpoint determined by the color of the respective comparison solutions. As observed by van Slyke *et al.* [41] the first appearing color change past the endpoint is not at all stable and comes in our experience about 0.5 to 1.0  $\mu\text{l}$  before the correct endpoint.

The titrimetric determination of bicarbonate is fast and well suited for routine analysis. The method gave a remarkable and unexpectedly high degree of reproducibility (coefficient of variation of 0.7).

#### Method used for comparison

The same original method for titrating bicarbonate as used above was compared (van Slyke *et al.* [41]).

### Bilirubin

Beckman/Spinco's modification (6076 B) of the method of Malloy and Evelyn [18] adapted for 10  $\mu\text{l}$  quantities is used.

#### Comments

Especially in pediatric clinical work it is of great importance to use a satisfactory bilirubin determination method. Most determinations made routinely are performed on immunized newborn infants in order to decide whether or not to make an exchange transfusion. This decision is usually made at a bilirubin level of 15 to 25  $\text{mg}/100\text{ ml}$ .

By using 10  $\mu\text{l}$  samples extinction values permitting more accurate readings for this level were obtained. The total volume became 10  $\mu\text{l}$  lower but no

compensatory addition was made in order to avoid another pipetting. The 10  $\mu\text{l}$  volume showed a better conformity with the macro method used and furthermore by using this volume only a total amount of 20  $\mu\text{l}$  plasma, if read against a standard curve, is required for determination of direct and total bilirubin.

The method shows good reproducibility especially at high levels of bilirubin where the coefficient of variation is 2.1. At a bilirubin level of 0.7  $\text{mg}/100\text{ ml}$  plasma the coefficient of variation is 7.3.

The method of Malloy and Evelyn did not follow Lambert Beer's law which also has been pointed out by Michaelsson [19].

Michaelsson and Nosalin [20] have developed a method which follows this law. This method has been adapted to microliter scale and preliminary tests with 5 microliter samples have shown good agreement with the aforementioned method. The standard curve obtained gave a straight line to a value of 30  $\text{mg}$  bilirubin/100  $\text{ml}$  plasma.

#### Method used for comparison

The method of Powell [30] was used.

### Calcium

Beckman/Spinco's modification (6071 B) of the method of Diehl and Ellingboe [7] is used.

#### Comments

The endpoint of the titration is difficult to determine; precision is obtained after practice and experience. Satisfactory light conditions are absolutely necessary and the titration is preferably

made in full daylight in order to get reproducible values. The eye-level of the investigator in relation to the position of the titration cup must be constant. To determine the endpoint the color of the sample is compared with a previously titrated standard. The sample has a yellow-green opalescence which makes the determination of the endpoint somewhat difficult.

Addition of thymolphthalein to the calcium indicator did not yield better results in this investigation. A sharp endpoint of titration can, however be obtained if the titration is performed in ultraviolet light. To shield from ultraviolet radiation and to facilitate the reading a special "viewer" can be attached to the titrator<sup>1</sup>.

The method has good reproducibility with a coefficient of variation of 1.6.

#### *Method used for comparison*

The method of Clark and Collip [3] was used.

### Chloride

Beckman/Spinco's modification (6072 B) of the method of Schales [35] is used.

#### *Comments*

The indicator is added during the stirring just before the sample is titrated. If the indicator is added earlier and mixed together with the plasma and nitric acid and the titration started afterwards there is a tendency of the indicator to get sucked into the tip of the burette and precipitate as a blue salt complex of diphenylcarbazone.

<sup>1</sup>Miles Instruments S. A., 26 Bd. Helvétique, Genève.

The titration is rapid with a sharp endpoint. The titration "viewer" may also be used to advantage in titration of chloride in ordinary lamp light. The method has a high degree of reproducibility with a coefficient of variation of 1.0.

#### *Method used for comparison*

The method of Brun [5] was used.

### Cholesterol

Beckman/Spinco's modification (6077 B) of the method of Caraway and Fanger [1] is used.

#### *Comments*

The method has poor reproducibility with a coefficient of variation of 5.5. The analytical values were about 10% lower than ordinary macro methods. Low values compared to macro methods such as were reported by O'Brien *et al* [96] were not observed. The solutions used must be freshly prepared for acceptable results. Concentrated sulfuric acid was used.

#### *Method used for comparison*

The method of Pearson, Stern and McGavack [98] was used.

### Creatinine

Beckman/Spinco's modification (6080 B) of the methods of Benedict and Behre [1] and Clark and Thompson [6] is used.

#### *Comments*

The method has a poor reproducibility with a coefficient of variation of 8.5. The obtained values were somewhat high compared to ordinary micro and



macro methods. O'Brien *et al* [26] suggest that the higher values are due to interfering chromogens but the major source of error lies in the low net absorbance and the many pipetting procedures with the microliter method.

In using the original microliter method O'Brien *et al* [26] found a coefficient of variation of 17.3. By changing the wavelength to 520  $m\mu$  and using the new type of pipette the coefficient of variation dropped to 4.1

#### Method used for comparison

The method of Teger-Nilson [38] was used.

#### Glucose

Beckman/Spinco's modification (6073 B) of the methods of Keston [14] and Teller [39] is used.

#### Comments

As pointed out by O'Brien *et al* [26] substantial errors may be introduced if only a single blank is prepared for analysis of several samples. A blank must be set up for each of the unknown samples. Otherwise a markedly yellow plasma will give too high value when compared to a blank made from a normal colored plasma.

The method shows a very low coefficient of variation of 1.1

#### Method used for comparison

The methods of Nelson [25] and Somogyi [36] were used.

#### Alkaline phosphatase

A microliter adaptation of the method for phosphatase determination described

by Bodansky [3] as modified by Natelson [21] is used

#### Reagents

Stock phosphorus standard. 40 mg P/100 mL.

Working phosphorus standard. 4 mg P/100 mL.

Buffered substrate. (Sodium beta glycerophosphate 500 mg/100 mL)

Trichloroacetic acid 20%

Acetic acid, 1 N

Molybdate acid

Reducing agent

#### Procedure

Add 10  $\mu$ l plasma to 100  $\mu$ l substrate. Incubate at 37 C for exactly one hour. Add 100  $\mu$ l 20% TCA mix well let stand 5 minutes and centrifuge 1-2 minutes. Transfer 100  $\mu$ l of the supernatant to a clean test tube add 50  $\mu$ l acid molybdate and mix. Add 50  $\mu$ l reducing agent and mix. Let stand for 30 minutes and read absorbance at 650  $m\mu$ .

The blank, standard and control are set up immediately after one hour has elapsed for the incubated sample.

**Blank** Add in the following order 100  $\mu$ l 20% TCA, 100  $\mu$ l buffered substrate and 10  $\mu$ l distilled water. Cap the test tube and mix immediately.

**Standard** Substitute 10  $\mu$ l of working phosphorus standard for distilled water and proceed as for blank.

**Control** Substitute 10  $\mu$ l plasma for distilled water and proceed as for blank.

**Calculations**  $\frac{\text{unknown}}{\text{standard}} \times 4 = \text{mg P/100 mL}$

Incubated plasma phosphorus - unin-

cubated plasma phosphorus = phosphatase in Bodansky units.

#### *Comments*

The method has been modified to use a 10  $\mu$ l volume of plasma. The incubation is carried out in a 400  $\mu$ l test tube. To stop the incubation 20% trichloroacetic acid is used. The absorbance is read at a wavelength of 650 m $\mu$ .

Natelson [1] claims that the extinction should be read at a wavelength of 890 m $\mu$  where the maximum of absorbance lies. This wavelength is not available on the spectrophotometer with its range of wavelength between 400 and 650 m $\mu$ . No absorbance maximum was obtained when the extinction of working phosphorus standard was determined at different wavelengths. The highest value of extinction was reached at 650 m $\mu$  and the readings were therefore taken at this wavelength. This is also used for the determination of phosphorus according to Beckman/Spinco.

#### *Method used for comparison*

The method of King and Armstrong [15] was used.

### **Inorganic phosphorus**

Beckman/Spinco's modification (6079 B) of the method of Fiske and Subbarow [9] is used.

#### *Comments*

The method is modified from a well-known macro method. The reproducibility is good with a coefficient of variation of 2.1.

#### *Method used for comparison*

The method of Taussky, Short and Kurzman [37] was used.

### **Potassium and sodium**

The method of Kaplan and del Carmen [13] is used.

#### *Comments*

The Eppendorf flame photometer is adapted for microliter measurements of sodium and potassium. The instrument is set on the highest level of sensitivity.

All material in contact with plasma is made of polyethylene and reagents are stored in polyethylene bottles. The diluting solutions are added by an automatic pipette. The samples are mixed slowly in an ordinary mixer.

The determination of sodium is rapid and has high reproducibility with a coefficient of variation of 0.8.

For the determination of potassium it is of utmost importance to use a plasma absolutely free from hemolysis. The amount of potassium in the red blood corpuscles is several times that of the plasma. The slightest degree of hemolysis will thus give remarkably high values of potassium at the determination. The method is fast and has good reproducibility (coefficient of variation 1.5).

#### *Method used for comparison*

The method for the analysis of potassium and sodium as presented in the Instruction Manual for the "EEL" flame photometer was used.

### Total protein

The method is a modification of the method of Weichselbaum [4<sup>o</sup>].

#### Reagents

- Biuret reagent (Weichselbaum)
- Dilute biuret reagent
- Ethyl ether
- Working protein standard

#### Procedure

Transfer 10  $\mu$ l plasma to a test tube and add 250  $\mu$ l dilute biuret reagent. Mix and read the absorbance after 10 minutes at a wavelength of 540 m $\mu$  on the spectrophotometer.

*Blank.* Omit plasma and add 10  $\mu$ l distilled water and proceed as above.

*Standard.* Substitute 10  $\mu$ l of working protein standard for plasma.

*Calculation*  $\frac{\text{unknown}}{\text{standard}} \times \text{protein in standard} = \text{g total protein/100 ml}$

#### Comments

The biuret reagent described by Weichselbaum [4<sup>o</sup>] was used instead of that of Gornall *et al.* [11]. Hereby one pipetting could be omitted by the exclusion of sodium sulfite.

The biuret reagent of Weichselbaum [42] contains more copper and sodium potassium tartrate and less alkali than the biuret reagent of Gornall *et al.* [11].

|                                       | Weichselbaum | Gornall |
|---------------------------------------|--------------|---------|
| CuSO <sub>4</sub> · 5H <sub>2</sub> O | 0.3          | 0.15    |
| NaH <sub>2</sub> tartrate             | 0.9          | 0.6     |
| N OH                                  | 0.8          | 3.0     |
| KI                                    | 5.0          | 0.1     |

To determine a serum protein concentration of g/100 ml Weichselbaum

[42] uses a final concentration of 140 mg protein/100 ml and Gornall *et al.* [11] 87.5 mg protein/100 ml biuret reagent.

Weichselbaum [42] has found experimentally that for values between 4 mg and 140 mg protein per 100 ml biuret reagent the extinction coefficient was constant. The microliter method used works with a protein concentration of 280 mg/100 ml biuret reagent.

The abrupt flattening of the standard curve at a level of 5 g protein/100 ml serum due to an error of the suggested ratio of Gornall biuret reagent to serum observed by O'Brien *et al.* [9b] was not encountered. The standard curve obtained gave a straight line to a value of 8.5–8.7 g protein/100 ml plasma.

It was found that the absorbance could be read after only 10 minutes instead after suggested 30 minutes with no change in results.

The method for protein determination proved to be time-saving and to give very good reproducibility with a coefficient of variation of 0.9.

#### Method used for comparison

The same original method for determining total protein as used above was compared (Weichselbaum [4<sup>o</sup>]).

### Albumin

The determination of albumin alone as one of the plasma proteins is of relatively little interest. With electrophoresis of a rather small plasma volume a clear pattern of the distribution of the different proteins in plasma can be obtained. The suggested microliter method includes a rather difficult transfer moment

which jeopardizes the accuracy of the method.

No statistical data are given as only a few preliminary studies were carried out with this method.

### Urea nitrogen

The method is a microliter adaptation of a urease method [44].

#### Reagents

Sodium tungstate 3.2%

Sulfuric acid 0.2 N

Nessler's reagent [97]

Buffer—28 g tetrasodium pyrophosphate ( $\text{Na}_2\text{P}_2\text{O}_7 \times 10\text{H}_2\text{O}$ ) is dissolved in 48 ml distilled water pH is adjusted with concentrated phosphoric acid and the volume made up to 50 ml with distilled water

Urease "Sigma Type V" (Approx. 000 Sumner units/g).

Buffered urease solution 6 units urease/ml buffer

Stock standard 50 mg N/100 ml (255.8 mg ammonium sulfate is dissolved in distilled water and the volume made up to 100 ml).

Standard curve is made by dilution of the stock standard.

Blank. Substitute 10  $\mu\text{l}$  distilled water for plasma.

#### Procedure

Transfer 10  $\mu\text{l}$  plasma to a 400  $\mu\text{l}$  test tube. Add in the following order—150  $\mu\text{l}$  distilled water 20  $\mu\text{l}$  sodium tungstate and 90  $\mu\text{l}$  sulfuric acid. Mix thoroughly let stand for 5 minutes and centrifuge. Transfer 60  $\mu\text{l}$  supernatant to a new test tube. Add 20  $\mu\text{l}$  buffered

urease solution. Mix and let stand for exactly 10 minutes at room temperature. Add 100  $\mu\text{l}$  icecold distilled water and mix. Add 150  $\mu\text{l}$  Nessler's reagent [27] and read absorbance after 5 minutes at a wavelength of 430 m $\mu$ . Calculate against a standard curve.

#### Comments

The initial urea method (Beckman/Spinco's modification (6075 B) of the methods of Fearon [8] and Friedman [10]) had a poor reproducibility and gave a coefficient of variation of 8.0. The cause of this poor reproducibility lies as had already been reported [96] in the error due to many pipettings of small volumes and the small net optical density.

O'Brien *et al* [26] found a coefficient of variation of 17.0 with Beckman/Spinco's method. The method was improved by increasing the period in the boiling water bath and the use of the new type of pipettes. The coefficient of variation thus obtained was 7.8. By using a urease method [97] they found the coefficient of variation to drop to 5.5.

The microliter urease method used in the present investigation gave a very good reproducibility with a coefficient of variation of 1.5.

#### Method used for comparison

The method of Nelson, Scott and Belfa [24] was used.

### Results

Microliter methods for the determination of bicarbonate, bilirubin, calcium, chloride, cholesterol, creatinine, glucose,

TABLE I

| Analytes                           | Microliter methods |                  |          |          | Routine methods |                  |          |          |
|------------------------------------|--------------------|------------------|----------|----------|-----------------|------------------|----------|----------|
|                                    | <i>n</i>           | $\bar{x} \pm s$  | <i>s</i> | <i>C</i> | <i>n</i>        | $\bar{x} \pm s$  | <i>s</i> | <i>C</i> |
| Bicarbonate, mEq/l                 | 14                 | 26.1 $\pm$ 0.03  | 0.17     | 0.7      | 20              | 36.1 $\pm$ 0.18  | 0.81     | 2.2      |
| Bilirubin, total mg/100 ml         | 31                 | 14.7 $\pm$ 0.1   | 0.31     | 2.1      | 20              | 2.20 $\pm$ 0.01  | 0.06     | 2.8      |
| Bilirubin direct, mg/100 ml        | 31                 | 0.73 $\pm$ 0.01  | 0.05     | 7.3      | —               | —                | —        | —        |
| Calcium, mg/100 ml                 | 20                 | 10.3 $\pm$ 0.04  | 0.17     | 1.6      | 20              | 12.5 $\pm$ 0.07  | 0.3      | 2.4      |
| Chloride, mEq/l                    | 15                 | 92.9 $\pm$ 0.23  | 0.87     | 1.0      | 20              | 106.9 $\pm$ 0.19 | 0.83     | 0.8      |
| Cholesterol, mg/100 ml             | 31                 | 197.0 $\pm$ 4.0  | 10.8     | 5.5      | 20              | 269.0 $\pm$ 3.1  | 14.0     | 5.2      |
| Creatinine, mg/100 ml              | 10                 | 1.18 $\pm$ 0.06  | 0.1      | 8.5      | 20              | 7.49 $\pm$ 0.18  | 0.82     | 10.9     |
| Glucose mg/100 ml                  | 16                 | 97.3 $\pm$ 0.27  | 1.1      | 1.1      | 20              | 77.6 $\pm$ 0.63  | 2.8      | 3.7      |
| Alkaline phosphatase units         | 27                 | 2.70 $\pm$ 0.03  | 0.16     | 6.0      | 20              | 18.1 $\pm$ 0.15  | 0.67     | 3.7      |
| Phosphorus, inorganic, mg/100 ml   | 23                 | 3.18 $\pm$ 0.01  | 0.07     | 2.1      | 20              | 3.30 $\pm$ 0.07  | 0.31     | 9.4      |
| Potassium mEq/l                    | 13                 | 4.95 $\pm$ 0.02  | 0.07     | 1.3      | 20              | 3.90 $\pm$ 0.005 | 0.02     | 0.3      |
| Protein, total, g/100 ml           | 31                 | 7.15 $\pm$ 0.01  | 0.07     | 0.9      | 20              | 7.12 $\pm$ 0.06  | 0.28     | 3.9      |
| Sodium, mEq/l                      | 20                 | 139.4 $\pm$ 0.26 | 1.14     | 0.8      | 20              | 129.3 $\pm$ 0.49 | 2.2      | 1.6      |
| Urea nitrogen (diacetyl) mg/100 ml | 31                 | 10.0 $\pm$ 0.28  | 0.8      | 8.0      | 20              | 7.52 $\pm$ 0.13  | 0.6      | 8.0      |
| Urea nitrogen (urease) mg/100 ml   | 16                 | 9.5 $\pm$ 0.03   | 0.12     | 1.3      | —               | —                | —        | —        |

*n* number of determinations,  $\bar{x}$  mean value, *s*, standard error (of the mean), standard deviation *C* coefficient of variation.  $C = s/\bar{x} \times 100$

alkaline phosphatase inorganic phosphorus potassium protein sodium and urea nitrogen were studied.

Of the 13 microliter methods investigated three were determined on the microtiterator (Ca Cl, HCO<sub>3</sub>), two were determined on the flame photometer (Na K) and the remaining eight namely bilirubin, cholesterol creatinine, glucose, alkaline phosphatase inorganic phosphorus total protein and urea nitrogen were determined on the spectro colorimeter. Under the comments of each method the experience with that method modification used and results are commented upon.

The mean value error of the mean standard deviation and coefficient of

variation of each analysis were evaluated by a large number of determinations on the same sample of plasma by the same procedure. The values are given in Table I

In testing the precision of some of the microliter methods adult plasma was used. The precision for all the microliter methods except those for alkaline phosphatase and potassium was found to be of the same degree or higher when compared to the analytical methods routinely used.

The result of the determinations made on the spectro colorimeter showed a lower degree of reproducibility compared to the other methods made on the micro titerator or flame photometer

TABLE 2.

| Analytes                            | Microliter methods |       |                      |      | Routine method |       |                      |      |
|-------------------------------------|--------------------|-------|----------------------|------|----------------|-------|----------------------|------|
|                                     |                    |       | expressed<br>in % of |      |                |       | expressed<br>in % of |      |
| Bicarbonate mEq/l                   | 22                 | 23.9  | 0.30                 | 1.3  | 18             | 28.5  | 0.5                  | 1.1  |
| Bilirubin, total, mg/100 ml         | 54                 | 5.70  | 0.20                 | 3.5  | 15             | 0.75  | 0.03                 | 4.0  |
| Bilirubin, direct mg/100 ml         | 54                 | 0.44  | 0.06                 | 13.6 | —              | —     | —                    | —    |
| Calcium mg/100 ml                   | 34                 | 9.48  | 0.14                 | 1.5  | 18             | 11.6  | 0.1                  | 1.2  |
| Chloride mEq/l                      | 65                 | 113.8 | 1.34                 | 1.4  | 15             | 107.4 | 2.09                 | 1.9  |
| Cholesterol, mg/100 ml              | 28                 | 151.7 | 10.6                 | 8.1  | 15             | 242.4 | 23.9                 | 9.9  |
| Creatinine mg/100 ml                | 16                 | 1.20  | 0.12                 | 10.0 | 15             | 4.37  | 0.75                 | 17.2 |
| Glucose mg/100 ml                   | 22                 | 77.4  | 8.0                  | 10.3 | 12             | 42.5  | 5.5                  | 13.0 |
| Alkaline phosphatase units          | 38                 | 7.19  | 0.34                 | 4.7  | 15             | 8.2   | 0.68                 | 8.3  |
| Phosphorus, inorganic, mg/100 ml    | 44                 | 7.21  | 0.14                 | 1.9  | 18             | 5.63  | 0.12                 | 2.1  |
| Potassium, mEq/l                    | 32                 | 5.87  | 0.05                 | 0.9  | 15             | 4.56  | 0.17                 | 3.7  |
| Protein, total, g/100 ml            | 40                 | 6.83  | 0.13                 | 1.9  | 15             | 8.00  | 0.17                 | 2.1  |
| Sodium, mEq/l                       | 36                 | 143.0 | 0.73                 | 0.5  | 15             | 137.2 | 2.92                 | 2.1  |
| Urea nitrogen (urease)<br>mg/100 ml | 37                 | 15.26 | 0.46                 | 3.0  | 15             | 19.3  | 1.63                 | 8.4  |

number of duplicate determinations;  $\bar{x}$ , mean value; error in methods =  $1/\sum d^2/2n$ ;  $d$ , difference.

Especially the methods of alkaline phosphatase, direct bilirubin cholesterol and creatinine showed high coefficients of variation. A contributory cause to this poor reproducibility lies in the very low net absorbance readings of these determinations.

Duplicate determinations were made on each analysis in order to evaluate the error of the method. The values for calcium, chloride cholesterol inorganic phosphorus and total protein have also been published in an earlier investigation [40].

In Table III the error of the method for the microliter and analytical routine determinations is given.

## Discussion

Until now almost every investigator working on microliter scale has developed his own equipment and used his own analytical methods.

The equipment used in this investigation was originally devised by Sanz [31, 32] and recently made commercially available by Beckman/Spinco. This equipment has been tested and used on the pediatric service for the past two years.

The Beckman/Spinco microtiterator proved to be a reliable rapid and accurate instrument. The present investigation confirmed the findings of Sanz [32] that the titration methods are more

accurate and faster than colorimetric methods. The results obtained seemed to be related to the speed of titration. This must be even and adequate. To estimate the suitable speed it was advisable to titrate a few standards before each set of plasma titration. The amount of light available and position of the technician in relation to the titrated sample were of great importance in determination of an accurate endpoint. A special "viewer" permits titration in ultraviolet light.

Colorimetric methods represent about two-thirds of all methods used in clinical chemistry. Reliable spectrophotometers have been used adapted for microliter measurements by using specially made micro cuvettes.

Sanz [31-32] and Seligson [31] have constructed spectrocolorimeters fitted with a special stationary cuvette which empties at the bottom. These cuvettes had a 10 mm light path and required about 75-100  $\mu$ l of solution for a reading.

The spectrocolorimeter used in the present investigation had only a light path of 6.4 mm and required a minimum volume of 100  $\mu$ l.

After using the instrument for some time the top layer of the metal cuvette holder scaled off due to the concentrated solutions used in microliter analyses. This disadvantage should easily be overcome by making the top of the cuvette holder of some other material.

A light but definite instability of the galvanometer was observed. It is questionable if the use of a stationary cuvette with all its advantages can overcome the disadvantage of short light path narrow

wavelength band, absence of a mirror on the meter scale and the slight instability of the instrument as pointed out by O'Brien *et al* [26]. At least in methods where the amount of color produced by certain reactions is small the combined disadvantages mentioned above may become a source of error.

The vital part in a microliter analytical system is the set of pipettes. The accuracy of these methods depends essentially on the precision with which the sample is pipetted.

Two types of pipettes are generally used namely constriction pipettes and overflow pipettes. The overflow pipette has the greatest precision of the two types but is wasteful of sample. Sanz [31] has constructed reliable microliter overflow pipettes made of polyethylene.

The microliter pipettes first supplied by Beckman/Spinco were not identical with those constructed by Sanz [31] as they did not have the drawn-out tip and were squarely cut at the end. The manufacturer is now supplying pipettes with drawn-out ends. Compared to the previous type of pipette, this one is less wasteful with material but somewhat difficult to inspect during the filling procedure because of the opaque dome. Original Sanz pipettes with high precision holding from five to more than two hundred microliters can be made in the laboratory from high grade polyethylene tubes of different sizes.

The Eppendorf flame photometer used in this investigation proved to be a reliable, fast and accurate instrument.

Setting the flame photometer for one standard for determination of sodium

TABLE 3 Comparison of different analysis' results expressed in coefficient of variation.

| Analyses                 | Analyst                        |          |                       | present study |
|--------------------------|--------------------------------|----------|-----------------------|---------------|
|                          | O'Brien, Ibbot<br>and Pinfield | Natelson | Caraway<br>and Fanger |               |
| Bicarbonate              | 6.3                            |          |                       | 0.7           |
| Bilirubin, total         | 5.3                            |          | 1.6                   | 2.1           |
| Bilirubin, direct        | 1.9                            |          |                       | 7.3           |
| Calcium                  | 1.5                            |          | 1.3                   | 1.6           |
| Chloride                 | 1.3                            | 0.9      | 1.0                   | 1.0           |
| Cholesterol              | 7.4                            |          | 2.0                   | 5.5           |
| Creatinine               | 17.3 (41) <sup>a</sup>         |          | 3.6                   | 8.8           |
| Glucose                  | 3.5                            | 2.1      | 3.3                   | 1.1           |
| Alkaline phosphatase     |                                |          | 1.7                   | 6.0           |
| Phosphorus, inorganic    | 1.6                            |          | 2.0                   | 2.1           |
| Potassium                |                                | .9       | 1.3                   | 1.3           |
| Protein, total           | 0.6                            | 3.1      | .8                    | 0.9           |
| Sodium                   |                                | 1.7      | 1.5                   | 0.8           |
| Urea nitrogen (diacetyl) | 17.0 (7.8)                     | 3.1      | 7.6                   | 8.0           |
| Urea nitrogen (urease)   | 5.3                            |          |                       | 1.3           |

<sup>a</sup>"New" type of pipettes used.

and making serial readings on the same solution of plasma showed a very slight tendency towards a progressive decrease in instrument readings. This finding was also encountered by Natelson [23]. This decrease was about 1% and could be eliminated by reading a standard with a similar concentration of the sample before and after the unknown solution.

The microliter test tubes made of polyethylene or polypropylene had an opaque color which presented some difficulty in observing minor degrees of hemolysis or slightly jaundiced plasma samples. The test tubes could easily be cut in two by a pair of scissors thereby facilitating the transfer procedure of plasma or serum without disturbing the contents.

The accuracy and precision of micro-

liter methods compared to micro or macro methods have been studied by many of the above-mentioned authors. Their findings [4-22] indicated that these methods were very satisfactory for clinical purposes although O'Brien *et al.* [26] preferred macro methods to microliter methods.

In order to compare the result of the present investigation with those obtained by the aforementioned authors, all values have been recalculated and expressed in terms of coefficient of variation. The data are listed in Table 3.

Microliter methods, though not particularly time-saving are as precise as macro methods. Neither the investigation by O'Brien *et al.* [26] nor the present investigation achieved as good a typical reproducibility as presented by the manufacturer in his pamphlet.



This may be attributed to the older model pipettes used in this study

The advantages of using microliter methods are evident. Small volumes are sufficient especially in the case of newborn infants acutely ill patients requiring repeated blood tests and small laboratory animals. Difficulties related to venipuncture and blood depletion are avoided by analyses on capillary blood. The small space needed for the equipment makes it very suitable for the general practitioner and hospitals with limited space. The remarkably low consumption of reagents reduces the cost of chemicals. The pipettes are made of plastic material and are unbreakable and longlasting. The test tubes and titration cups need no cleaning and once used they are discarded. The equipment can after suitable training, easily be handled by anyone with good analytical results. Most macro methods can be modified to microliter scale.

### Summary

A comparison is made between routine chemical methods and the methods

in microliter scale as developed by Sanz [31-32].

All analyses were made on the Beckman/Spinco Ultramicro Analytical System except for the determinations of potassium and sodium which were analysed on an Eppendorf flame photometer.

Methods for bicarbonate alkaline phosphatase and urea nitrogen were developed and available methods for determination of bilirubin cholesterol and total protein were somewhat modified.

It was found that the microliter chemical determinations are sufficiently accurate for clinical work and have the advantage of requiring less blood.

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Apexcardiography phonocardiography  
and ballistocardiography —

SUPPLEMENTUM 404

APEXCARDIOGRAPHY PHONOCARDIOGRAPHY  
AND BALLISTOCARDIOGRAPHY —  
THEIR DIAGNOSTIC  
AND PROGNOSTIC SIGNIFICANCE IN  
CORONARY HEART DISEASE

BY  
KARL RÖRVIK

*Accompanies Vol 174*

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Apexcardiography, phonocardiography  
and ballistocardiography —  
their diagnostic  
and prognostic significance in  
coronary heart disease

By  
KARL RØRVIK

UNIVERSITETSFORLAGET

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## Preface

This work was planned during my appointment at Ullevål Hospital, Department VIII.

I should like to express my heartfelt gratitude to my former chief Professor Carl Müller for his trust and unfailing interest in the project. His support has been of decisive importance for the realization of this work.

The investigation itself was carried out at Aker Hospital, Medical Department A, and I am especially indebted to Professor Røald Opsahl, head of the department. His interest in this work and his sound advice and encouragement were of inestimable value.

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Ullevål Hospital, Dept. Solvang,

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## CHAPTER I

### Introduction and plan of study

Clinical examination of the heart in coronary heart disease very often yields doubtful or negative findings. Excluding the acute stage of cardiac infarction, positive findings are mostly dependent on whether the disease process has resulted in cardiac hypertrophy enlargement, or failure.

On inspection and palpation abnormal precordial pulsations, if present, may be revealed. However the reliability of these findings will depend to a considerable extent on the skill and experience of the examiner. All too often findings will be doubtful. In addition less prominent pulsations can easily be overlooked even by the most experienced.

On auscultation, positive findings in coronary heart disease are also present less frequently than in some other forms of cardiac disease. Demonstration of a diastolic gallop in a patient with incipient cardiac failure is an important finding. The appearance, under certain circumstances, of a diagnostically significant

change in the strength and character of the 1st heart sound over the apical area, has been reported in the literature. The auscultation findings referred to, however are often difficult to hear or difficult to assess.

Electrocardiography is the investigation which has proved to be the most reliable in the diagnosis of coronary heart disease. However this method all too often gives doubtful or misleading results. In addition, it is almost entirely of diagnostic significance and does not, in itself yield much information on cardiac function or prognosis in actual cases examined.

Considerable information as regards cardiac function may be obtained indirectly by demonstrating radiologically a definite cardiac enlargement, and even more so by comparing radiological findings with results of clinical examination. The value of radiological examination is lessened, however by the great normal variability in cardiac size. As a result,

normal limits are all defined and in a relatively large number of cases no definite information can be obtained as to whether or not the heart is enlarged.

These circumstances have promoted a search for easy and harmless methods to improve diagnostic precision in coronary heart disease and to assess the severity of the disease, the cardiac function, and prognosis.

The opinion has been held widely supported by numerous encouraging publications, that ballistocardiography might be the method which could thus complement electrocardiography. For various reasons, however doubt has persisted as to whether the method is of any great value in this respect.

Using suitable apparatus, graphic recording of normal and pathological precordial pulsations can be obtained, though choice of method and apparatus is debatable. This investigation is called cardiograph or kinetocardiography and registration of the apical impulse is called apexcardiography. This method is easy to use and seems in many cases, judging from reports in the literature, to give us essential information as regards the condition of the heart.

Phonocardiography as is well known, provides in many cases a good support for the auscultation findings. There has been only slight interest, however in phonocardiographic findings in coronary heart disease.

In the present work the author aimed at investigating

findings which can be obtained on precordial palpation and auscultation in coronary heart disease and whether they can give positive information where clinical examination of the heart is negative or gives equivocal results.

2. Whether simultaneous use of these two methods together with ballistocardiography can yield valuable information on the patient's condition in other respects, and furthermore whether the results of one or more of these methods of investigation allow us to draw conclusions of prognostic importance.

The plan of study which has been followed in the investigation can be outlined briefly as follows:

A control series is used for the purpose of obtaining the most reliable basis possible for evaluating normal findings and their separation from the pathological. In doing this special emphasis has been laid on working out a very careful and accurate technique and apparatus, both as regards ballistocardiography and apexcardiography. Following systematic and thorough examination of the normal series by usual methods — clinical electrocardiographic, and radiological — these investigations have been supplemented by the three additional graphic methods referred to above.

A series comprising patients with coronary heart disease is then studied in the same way and by the same methods.

Finally results obtained in patients are compared with those of the normal controls, and an account is given of the conclusions drawn.

1. Whether apexcardiography and phonocardiography can provide an objective and reliable representation of the

## General aspects of the clinical examination of the heart in coronary heart disease

Inspection, percussion, palpation, and auscultation, remain our methods in clinical examination of the heart. Auscultation is the most important as regards the anatomical and etiological diagnosis. However its value in this respect tends to diminish in a population in whom atherosclerosis and hypertension are assuming predominance amongst etiological factors (White 1953)

In the present work, emphasis will be placed mostly on palpation and auscultation, whilst inspection and percussion will only be discussed briefly

### 1. INSPECTION AND PERCUSSION

Inspection of the precordium under normal conditions may yield information as to localization of the apical impulse, though the actual incidence is uncertain. On careful inspection in adequate light, one may observe at times a slight systolic retraction near the apex or just to the left of the lower part of the sternum, especially when cardiac action is forceful or in thin, flat-chested subjects.

Under pathological conditions — which in this connection means coronary heart disease — percussion may reveal enlargement of cardiac dullness on the precordium to the right or left or in both directions.

In the presence of a more severe degree

of left ventricular hypertrophy and enlargement, a laterally displaced, more or less prominent and broad apical thrust, will very often be visible. In these cases one may actually see that the apical thrust persists longer than usual, throughout the greater part of systole, as an expression of its heaving quality. In some cases one may observe, besides the apical thrust, a diffuse heaving impulse in larger areas, or of the entire left precordium extending from the apex region towards the lower part of the sternum, which will also show movements if there is a concurrent marked degree of right ventricular enlargement.

One must emphasize, however that in the older age groups, to which most patients with coronary heart disease will belong, considerable cardiac hypertrophy and enlargement may be present, although visible pulsations are very small or absent, and findings on percussion will frequently give no definite information. This is especially true in patients who have a so-called barrel-shaped thorax and even more so where the cardiac disease is accompanied by significant emphysema or adiposity

### 2. PALPATION

The precordial pulsations as they present themselves by inspection and palpation



have attracted the interest of clinicians from ancient times. In particular this concerns the apical beat and its position in relation to the midclavicular or the mamillary line or its distance from the midsternal line.

There is general agreement that the apical beat is located normally within the mamillary line or midclavicular line (4 11 18 36 70 92, 113) or at any rate not beyond this line (39). White (1951) draws attention to the fact that pregnancy and abdominal distension normally may displace the apical beat, which can be palpated slightly outside the midclavicular line and more cranially than usual. The exact position of the midclavicular line however is not easy to determine and the mamillary line is not very useful in women.

Ten centimetres from the midsternal line is the limit of normal usually quoted by those who prefer to measure the distance from the mid line (90). Lewis (1946 p 119) maintains that the apical beat must be at least 11 cm to the left of the mid line or well outside the mamillary line, before it can be accepted as definite evidence of cardiac enlargement. This sign is more conclusive if the apical beat is located in the sixth intercostal space, than in the fourth. In any event, the heart itself is assumed not to be displaced to the left. Cornerbeare (1942) maintains equally strict criteria. Isaac & Lewy (1951) found the apical beat to be situated more than 10 cm to the left of the mid line in as many as 45 out of 395 young male adults (11.5 per cent).

One must be extremely cautious in diagnosing cardiac enlargement in children and young adults on the basis of

finding an apical beat situated just lateral to the mamillary line (50, 105 109). This is true in all age groups if the ictus is located in the 4th intercostal space (55).

The apical beat is usually considered to be due to the part of the left ventricle situated just to the right of the cardiac apex. Many clinicians therefore consider palpation of the lateral border of the point of maximal impulse to be the best guide of cardiac size (70, 90 105 109), whilst others, for practical reasons, prefer the centre point of maximal impulse (4 56 87 113).

The frequency with which the apical beat can be localized under normal and pathological conditions is of great importance. Authors discussing this question maintain mostly that the apical beat can be palpated in the majority of normals or in nearly all (18 79 109 113). Reservations are made in the case of obesity, emphysema, barrel-shaped chest, and age. Few systematic investigations have however been carried out on this point. Isaac & Lewy (1950) examined a random sample of 500 young men average age 21.5 years, and were unable to palpate or locate the apical beat in 105 cases. Niehaus & Wright (1945) examined 1000 apparently healthy persons, both male and female, and found a palpable apical beat in 54 per cent of the men and 55 per cent of the women up to the age of 20 years. This percentage fell to 27 and 39 respectively between the age of 20 and 30. Increase in weight was accompanied by a rapid decrease in the incidence of palpable apical beat. It was palpable in 24 per cent of all age groups considered together and was not palpable or could not be located in 76 per cent.

These results support the experience that the apical beat can usually be palpated in children and young adults, but this becomes more difficult with increasing age. Palpation is naturally easier and thrust more prominent in subjects with a long flat chest, than in those with a deep barrel-shaped chest. The considerable variations in statements regarding the incidence with which the apical beat is palpable are presumably due in part to the fact that the examination is carried out in different body positions. The apical beat is easier to palpate in an upright position (87) especially with the subject seated and the thorax inclined slightly forward (109), than when lying supine. This may however be accompanied by a change in position of the apical beat (50), and in slightly prone position of the body presumably also by a change in its character. This is true, at any rate, on palpation in left lateral position.

Palpation of the apical beat with the subject lying supine and flat, or with the upper body slightly to moderately elevated, is considered by the author to be the best method for many reasons. An apical beat covered and unpalpable behind a rib may be brought into an intercostal space by slight raising or lowering of the upper body.

Lack of uniformity in results may also be partly due to different techniques of examination. Correct technique is very important (Dressler 1959 Warburg 1956), though the experienced examiner may well develop his own method.

Also the incidence of palpable apical beat must be anticipated to be different in patients and in normal controls.

The character of the apical beat has

been the subject of less attention than its position.

The normal apex beat comprises a short small thrust, of sudden onset and disappearance, and is usually confined to the first part of systole. It may be palpable during most of systole in some young or thin subjects, especially on exerting some pressure with the palpating hand or finger but the initial sudden thrust still predominates. The characteristic sudden decrease in the force of the impulse can usually be felt clearly. This applies also in cases with augmented cardiac action and prominent apex beat, following manual work, in thyrotoxicosis, fear high fever etc.

The heaving ('resistant lifting') apical beat by contrast is not dominated by the initial sudden thrust, but can be palpated evenly throughout the whole of systole, or is found to be somewhat increasing, or decreasing in intensity towards the end of systole.

General agreement exists that demonstration of a heaving apical beat is evidence of cardiac hypertrophy either isolated hypertrophy of the left ventricle or combined left and right hypertrophy. Isolated right ventricular hypertrophy and dilatation can hardly result in a localized heaving impulse in the apical region, but may presumably give a diffuse heaving impulse over the entire area from sternum towards apex (Warburg 1956).

Dressler (1950) states that a markedly enlarged right ventricle will cause a distinct pulsatory bulge over the precordium. The pulsation is most marked along the left margin of the sternum between the third and sixth ribs. It may extend over the lower half of the sternum

and slightly beyond it to the right. At left it reaches occasionally the left mid clavicular line

This so-called left sternal lift is often to be seen by inspection. It can better be felt, however especially if one presses the base of the lightly dorsiflexed hand against the area to be explored.

### 3 AUSCULTATION

Excluding arrhythmia and pericardial friction in the initial acute stage of cardiac infarction, auscultation infrequently reveals findings of diagnostic importance in coronary heart disease. If present, however positive findings are of considerable significance, as they may be the first and only clinical sign of impending cardiac failure.

A diastolic gallop either protodiastolic or presystolic, is the sign preferably to be sought for. The 3rd and 4th heart sounds and their corresponding gallop are soft and of low frequency and are therefore often inaudible or difficult to detect. Individual variability among clinicians is also a factor to be taken into consideration. The ability to hear these weak heart sounds depends on experience, different hearing threshold, stethoscope used and noise in the surroundings.

An audible 3rd or 4th heart sound in middle-aged or older patients is practically always pathological and as a rule

implies imminent or manifest cardiac failure. A presystolic gallop is difficult to detect, however with normal atrio-ventricular conduction, and it may be difficult to decide whether the third sound in an audible triple rhythm is, in fact, presystolic and not systolic.

A considerably reduced intensity of the apical 1st heart sound is a sign which may be of importance and has been stressed as significant especially by Boas & Boas (1949). Concomitant with the decrease in loudness, the 1st sound often assumes a muffled character. This sign is subject to a much greater degree of subjective assessment than the other auscultation findings referred to, and there is a definite danger of over-diagnosing. In many cases, however there is a characteristic dissociation of loudness of the two apical heart sounds, the 1st sound being distant and dull whilst the 2nd sound may be relatively loud. In extreme cases the 2nd sound only may be heard at the apex. Such a finding is especially typical when present together with a heaving and possibly laterally displaced, apical thrust.

The auscultatory findings mentioned are encountered fairly often during the acute stage of myocardial infarction and are considered to be due to a weakening of the myocardium, but they may be heard quite commonly also in cases of coronary heart disease with a marked degree of left ventricular failure, or in cases of myocardial aneurysm (Boas & Boas, 1949 pp. 246 and 258).

## CHAPTER III

### Graphic recording

#### 1. REGIONAL CARDIOGRAPHY

Attempts to obtain information of value in diagnosis by graphic recording of precordial pulsations have been made for nearly a century. Marev and Potam (57), Frank (29-30), Hess (43), Weitz (108), Wiggers (111), and Weber (107) are amongst those connected with developments in this field.

Graphic recording of precordial pulsations is termed cardiography or regional cardiography. Interest has been especially centred on the registration of the apex beat — the so-called apexcardiography

##### a) Requirements for equipment

The earliest instruments were, in technical respects, rather deficient.

Frank's construction of his segment capsule in 1903 represented a great advance. It eliminated important sources of error which hampered earlier equipment (mechanical weight and inertia of the recording parts, low natural frequency and frequency response, considerable limitation of amplification possibility). However Frank's capsule too was hampered with defects, amongst others time lag due to length of air transmission, and it never attained widespread use, presumably owing mainly to the fact that the equipment was complicated and cumbersome to use.

Electrical methods of registration were

introduced as Miller & White (1941) constructed their crystal microphone. It has been used to some extent in the United States either in its original form, or with minor modifications of application and type of pick-up.

Miller & White used a small cup, with balloon section to obtain airtight application to the chest wall. A small rubber tubing provided air transmission of the pressure variations to the microphone, which transformed the mechanical pulsations to equivalent electrical impulses. These were recorded by an ordinary electrocardiograph.

Brecht & Boucke (1952) constructed a condenser microphone for similar purposes.

It consists in principle of several elastic, pliable, flat condenser coils, lying on each other and insulated against each other by leaf-thin molanion foil covered with fine powder. The entire arrangement is enclosed in a small casing. The microphones tolerate considerable and long acting pressure, without being damaged. It is applied directly to the chest wall, with no intervening air transmission. Impulses are transferred to the microphone by means of a feeler pin or small plate. The endpiece is placed against the chest by a metal bar attached to a non-yielding frame fixed to the bed. The coupling to the electrocardiograph is made by means of so-called pulse wave attachment. Two microphones may be used simultaneously and have each an independent amplitude control.

The apparatus is very sensitive, much more than required for recording of precordial pulsations. Damping and frequency range are both satisfactory. The frequency curve shows line

arity between 0.3-150 cycles per second. The natural frequency is 500 cycles per second. The endpiece is surrounded by a protective metal frame to avoid any unexpectedly high pressures acting directly on the pressure receiving surface of the receptor

In modern equipment, many of the deficiencies inherent in older types of apparatus are avoided. No difficulties are encountered with respect to frequency response, speed of deflection, natural frequency damping, or amplifying capacity. Time lag can be avoided and, last but not least, the equipment is easy to use. Especially former problems of transmitting impulses to the recording apparatus can be avoided. However a new problem is presented, that of the time constant.

Miller & White state that the microphone should have a time constant of several seconds. This represents so far no difficulty either concerning the crystal microphone or the condenser microphone. The final result is, however in this respect, dependent on the properties of the electrocardiograph, as the combined time constant of several systems joined in series is less than the smallest time constant of a single link in the chain (5).

The question of which method for application of pick-up is the correct one has attracted surprisingly little interest, in spite of the fact that there are several methods in use, and one must anticipate that difference in method of application can lead to differences in type of wave form, which may even be decisive.

The following methods were used, in cases where type of application was mentioned. Application to pulsating point

by means of a suction cup (58) pick-up held in place by means of an elastic band around the chest (53 107 108) rigid fixation using a bar attached to a stand or similar object, and projecting perpendicular towards the chest (2, 43 107) or using a crossbar (27)

Petter (1908) considered this point theoretically with reference to the sphygmograph and maintained that rigid fixation was the only right method, as did Wiggers (1923) who maintained that one should adjust the apparatus so that its body is absolutely rigid as compared to the artery beneath. This in spite of the fact that arterial compressibility is a problem, actual in pulse wave recording (6 19 45) but not in cardiography. Wiggers stated that elastic fixation or suspended application has the decided drawback that the body of the apparatus itself may be set in motion. Petter contended that even the elasticity of the ordinary bands of some forms of sphygmographs adds materially to their inaccuracy.

Eddleman *et al.* (26) discuss this problem and are of the opinion too that a rigid fixation of the pick up device must be used, and say that any device resting primarily on the chest wall will not record, or will minimize the movements that the entire chest or part of it makes, registering only the relative movements.

The role played by the size of the endpiece when bellows are used, and thickness and tension of the membrane, when using a membrane type of endpiece, has not been clarified, though Eddleman *et al.* (27) tried several types of bellows. Its diameter may perhaps play a part when a cup or funnel type of endpiece is used (26).

b) *Earlier investigations with modern instruments terminology and some results*  
The normal apexcardiogram was considered, for a long time, to be typical only if it presented a positive plateau-like wave during systole (52). Later studies, with better techniques, have elucidated this point and clarified the main trends in the normal tracing, even though attention has been called to the considerable normal variations.

The apical tracing was found early on to vary in appearance according to whether the subject was sitting, lying flat, or lying on the left side (43-107). Moreover major changes in the wave form were observed with minor changes in the position of the pick-up on the chest wall in relation to the apical beat (111). However as will be discussed later this finding is hardly of any consequence as regards differentiating between a normal and pathological tracing.

It is extremely important, on the other

hand, not to compare results of investigations on patients sitting up or lying on their left side with those obtained from patients lying supine, irrespective of correct and irreproachable technique.

Though Lusada & Magni (1951) stated that the movements of the heart are particularly well recorded over the apex when the subject is either lying on his left side or sitting they made their investigations with the patients in a supine or semirecumbent position. They used a short funnel fixed to the required site by means a rubber band around the chest. Precordial and epigastric pulsations were recorded by air transmission to a crystal microphone, and phonograms were registered synchronously by a stethoscopic microphone.

Lusada & Magni (53-54) as did previous authors (107-108) described the different waves seen in the cardiogram, their appearance and course, and denominated the more important ones (Fig. 1)

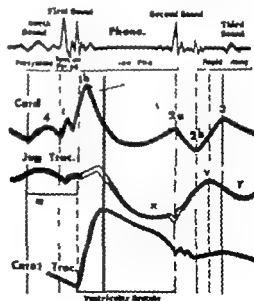


Fig. 1 Low-frequency tracing of the apex (Card) compared with phonocardiogram, jugular tracing, and carotid tracing. Dotted line indicates possible variant.

From *Cardiology* (Editor A. A. Lusada)  
McGraw Hill-Blakiston, 1959

A double wave observed at the start of systole was called 1a and 1b. An inversion of the curve or a systolic plateau follows during systolic ejection, 2a and 2b referring to the waves at the end of systole. Two more distinct waves occur in diastole: the rapid filling wave in protodiastole, wave 3 (3rd sound) and the atrial wave in presystole, wave 4 (4th sound).

They found

1) that the following pattern indicates left ventricular preponderance due to dilatation or hypertrophy. A high systolic pulsation at the apex assuming the aspect of a plateau lasting during the entire systole, or that of a high, peaked wave during early systole, followed by a depression during the second half of systole. The epigastric tracing reveals a deep depression during most, or all, of systole.

2) that the following pattern indicates a predominant enlargement of the right ventricle. A high positive wave of the epigastric tracing during the first half of the systole combined with a deep depression of the tracing at apex during the entire systole.

3) A positive thrust both at the apex and the epigastrium may be interpreted as the result of simultaneous enlargement of both ventricles, causing extensive contact of the heart both with the chest wall and the diaphragm.

A plateau wave was found, as mentioned, to occur in the normal apexcardiogram. It is evident that the value of apexcardiography as a method of investigation will depend on whether and to what extent, normal and pathological tracings can be differentiated.

Harrison and co-workers have described their investigations of precordial pulsations in a number of articles. They use a slightly modified technique, and prefer the term *kinetocardiography* instead of *cardiography* or *regional cardiography*. The technique employed is described by Eddleman *et al.* (27).

They use metal bellows that transform chest wall movements into a pulse wave in an airtight system, which in turn is transformed by a piezoelectric transducer into an electrical current. Attached to the bellows is a small metal arm which has a flat endpiece 7 mm in diameter that is placed against the chest wall. The entire bellows and pick-up piece can usually be mounted on a crossbar and, with the use of a universal type clamp, the endpiece can easily be applied perpendicular to any place on the chest from which displacement records are desired. Almost any type of electrocardiographic apparatus can be used as a recorder. Records are obtained in positions on the chest wall which correspond to the conventional precordial electrocardiographic leads,  $V_1$  through  $V_6$ .

In common with others, they found that normal variations occur in the recorded tracings and they described three types of curves recorded in  $V_1$ ,  $V_2$  and  $V_4$ - $V_6$  positions: Types I, II and III (26), which differ mainly in systole. Type I was found in 78 % of persons examined, type II in 14 % and type III in 8 %. They never observed a systolic plateau, as described by Lunsada & Magri, under normal conditions and they attribute the difference to the fact that they used a pick-up device fixed at a point unconnected with the subject, in contrast to Lunsada & Magri's method of elastic fixation. The latter however consider the discrepancy to be due to the difference in pick-up device (54).

Harrison and co-workers use a more comprehensive, though more complicated, nomenclature (Fig. 2). Both positive and negative waves are lettered and numbered, I referring to waves in the isometric phase of systole, and E to waves in the ejection phase. Protodiastolic waves are termed D and presystolic A.

This nomenclature will be followed in principle in this work, though with some modifications.

## 2. PHONOCARDIOGRAPHY

Diastolic gallop sounds can easily be demonstrated with the aid of modern phonocardiography. A presystolic gallop may be identified by concurrent electrocardiography. Simultaneous recording of an apexcardiogram enables differentiation in doubtful cases, between, for instance,

a protodiastolic gallop and an opening snap (48 52 65).

Objective phonocardiographic representation of changes in strength and quality of the 1st heart sound, and alteration of the relative strength between 1st and 2nd sound at the apex will, however no doubt be much more difficult and uncertain. It is at present difficult from a phonocardiogram, to distinguish between cardiac and extracardiac causes of faint heart sounds (emphysema, obesity etc.) A marked difference in the intensity of 1st and 2nd sound at the apical area may be of help, the 1st sound being very faint, the 2nd loud. But an accentuated 2nd sound occurs frequently in cases of hypertension, aortic sclerosis, and syphilitic aortitis, and it is difficult to judge from a heart sound tracing whether the 1st sound is enfeebled or the 2nd sound is pathologically accentuated.

Fig. 2. Schematic drawing of kymocardiograms taken from V and V<sub>1</sub> position. The nomenclature is based upon modified division of the cardiac cycle. Both the peaks and the valleys of waves have been named. I I are points of waves that occur during the phase of isometric contraction, E E<sub>1</sub> points during ejection systole. Movements during diastole are indicated by the letter D and movements during auricular systole by A.

(From Eddleman, E. F. J. et al. 'The Kymocardiogram. II. The Normal Configuration and Amplitude' *Circulation* Vol. VIII, p. 271 1953. Reproduced by permission of the American Heart Association and the author.)





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hypertension is defined as a systolic blood pressure above 170 mm Hg without elevated diastolic blood pressure. The patient material is divided into three groups on the basis of these criteria

1. Normotensive.
  - a) Hypertension never demonstrated.
  - b) No hypertension found though records prior to appearance of coronary heart disease not available.
2. Hypertensive.
  - a) Slight or intermittent hypertension, usually labile, diastolic pressure never above 120 mm Hg.
  - b) Severe or persistent hypertension, with diastolic pressure constantly elevated to levels usually exceeding 110-120 mm Hg.
3. Systolic hypertension.

#### *Precordial palpation*

Palpation was carried out along the lines recommended by Dressler (1959) which are as follows

Palpation is performed by the examiner standing at the right side of the patient and placing his open hand over the precordium. In order to detect an apical thrust, the index and middle fingers are pressed firmly against the apical region. Sometimes it is necessary to exert considerable pressure in order to detect an apical thrust hidden by a broad, melastic rib. Thrills are best felt with the hand resting lightly on the precordium. Pulsatory phenomena other than the apex beat, such as the heaving pulsation of the precordium caused by enlargement of the right ventricle, are elicited by pressing

the base of the lightly dorsiflexed hand against the area to be explored

The frequency with which the apical beat could be localized was recorded for the patient and normal material. The apical beat was not considered palpable in cases where some pulsation was found in the apical area but not definite enough to locate the site of the apical impulse. The site of the maximal impulse was used, not its lateral border

A probable or definite heaving apical beat was registered and graded

Grade I Probably slightly heaving.

Grade II Moderate and definitely heaving.

Grade III Usually diffuse and strongly heaving.

#### *Auscultation*

On auscultation, the author tried to evaluate whether loudness and quality of the apical heart sounds could be of diagnostic significance in conjunction with phonocardiographic investigations. Cases were registered, tentatively in which dissociation of loudness of 1st and 2nd apical heart sound was found, the 2nd sound being considerably louder and the 1st sound weak. Any slight or markedly accentuated 2nd sound over the aortic valve was also noted, and coincidence of these two findings may be thus investigated. Systolic murmurs heard over the apex were noted, excluding short soft murmurs which rarely affect the loudness of either 1st or 2nd apical heart sound. Subjects with a diastolic murmur are excluded from this material. Incidence of audible gallop rhythm was also noted and compared with results of phonocardiography

## Cardiac failure

This was evaluated on the basis of clinical history and findings, and graded according to the New York Heart Association's criteria (62)

Cases are classified into left heart failure, and combined left and right heart failure.

## 2. THE RECORDING EQUIPMENT

### a) *Electrocardiography*

The registering instrument used was a direct writing, four channel electrocardiograph, Eterna Schönanders Mingograph 43

The recording principle is that a very fine jet of ink is impelled at high speed from minute nozzle. This means that the galvanometer system has a very small inertia. The manufacturer claims linear response to about 500 cycles per second. The time constant is 2 seconds.

The apparatus has four fully independent amplifier channels. Each channel is also provided with separate a-c and d-c input circuits for special recordings. There are six paper speeds, which can be preset or changed during operation.

A twelve-lead electrocardiogram was taken in each case: the standard limb leads, the augmented unipolar leads, and the unipolar precordial leads  $V_1$  through  $V_6$ .

Sokolow & Lyon's criteria (91) were used in electrocardiographic diagnosis of left ventricular hypertrophy

### b) *Phonocardiography*

In the accompanying Heart Sound Amplifier type 42 A the heart sound is split into six frequency ranges or bands, the maximum intensi-

ties which correspond to the nominal frequencies 12 - 25 - 50 - 100 - 200 - 400 cycles per second. Besides the six frequency bands there is a band with a frequency response corresponding to the human hearing impression. By means of a calibrator the amplifier + galvanometer can be checked.

Phonocardiography of the apical area was carried out routinely, using three frequency bands: 25 cycles per second, 100 cycles per second, and the aural band. Following this, synchronous recording of precordial pulsations and phonogram was taken, using the 25 cycles per second band, to demonstrate possible gallop sounds. The last mentioned phonographic recording was made in the third left intercostal space in the parasternal line, and not over the apex, due to lack of space. With the microphone in this position, gallop sounds may not be visible in spite of their presence in the apical area.

Constant amplification was used, irrespective of the loudness or weakness of the heart sounds. Amplification was set as high as advisable in considering the necessity of avoiding noticeable disturbances in the tracing due to muscle tremor or other noise from extracardiac sources.

### c) *Regional cardiography*

Precordial pulsations were recorded using the condenser microphone earlier described (see p. 15)

Two endpieces may be used. Each endpiece mounted on a metal bar is pushed perpendicularly against the points on the chest wall to be explored. The bar is fixed onto a light but rigid frame, constructed by the author which is kept attached to the ballistocardiographic bed by a locking device.

Time constant of the microphone used is 5 seconds. By coupling to the electrocardiograph a-c amplifier the resultant time constant of the equipment is changed to 1.5 seconds.

Sensitivity is considerable, and amplitude can be increased or decreased stepwise well beyond the required range.

Calibration of the apparatus seems to be a relatively simple matter. A special apparatus was constructed for this purpose consisting of a motor-driven eccentric, which moves a bar back and forth through a known distance so as to produce a sine wave. This method was also used and described more fully by Eddleman *et al* (27).

However the condenser microphone used in the present study is to be applied on the chest wall with some pressure. Movements during calibration are transferred to the microphone by a rigid object, whereas the chest wall is softer and more or less compressible. A simple test showed convincingly that a certain amount of pressure was required to compress the condenser microphone. In other words, resilience of the soft tissue may play a part, in so far as precordial movements of a certain size do not necessarily result in the same excursions as when movements of equal size originate in a calibrator with a different consistency. This was found to be the case in all probability and calibration was therefore not carried out. Absolute size of precordial pulsations, in fact, with very few exceptions, is less important than the shape of the curve and the interrelationship between size of individual waves in the curve.

The absolute size of the apex beat is, however easy to determine by means of a reliably calibrated ballistocardiograph (the magnet-coil principle)

A small alnico bar magnet ( $6 \times 1$  cm) is placed perpendicularly on the chest wall with one end against the apex beat, and is held in position with a rubber strap. The coil is fixed outside the body and is positioned so that the magnet moves freely in the coil field at each heart beat. Size of beat is obtained directly in microns on recording the displacement tracing (see later) a typical percardiogram is then obtained.

A palpable apex beat, but not an especially prominent one, yielded impulses of around 250 microns. Considerably lower values were obtained on the calibrated condenser microphone. Amplitudes were considerably greater when the magnet was pressed hard against the apex beat than when applied more lightly as was the case with the condenser microphone also, and which may be anticipated by clinical experience. The shape of the curve obtained was unaltered in either case. The great variability in magnitude of waves, dependent on pressure of application, will also affect the value of calibration as long as the degree of pressure and compressibility of chest wall are not known.

Regional cardiography was carried out systematically from two places, over the apical area and at the left sternal margin. In a few cases recordings were also made from the area in between.

Apexcardiogram was recorded at the point of maximal impulse, where the apex beat could be localized. In other cases the endpiece was applied to the 5th intercostal space a finger's breadth within the mamillary line, and recordings were taken from that point.

The other endpiece was applied at the left sternal margin in the 5th intercostal space, this point being situated approxi-

mately in the middle of the pulsatory bulge which may be encountered in cases with markedly enlarged right ventricle and is usually referred to as the left sternal lift (see p. 13)

### 3 Radiological examination

Relative cardiac volume ( $\equiv$  volume per  $m^2$  body surface) was calculated by Jonsell's method (49). A relative volume of up to 450 ml is taken as normal in this study which does not include women. Cardiac enlargement is considered to be present when the relative volume exceeds 500 ml, and possible enlargement at relative volumes of 455-500 ml.

The examination aimed, in addition, at deciding whether findings indicated

1 Isolated enlargement or enlargement chiefly of the left side of the heart.

2 Generalized cardiac enlargement.

The radiological examinations were performed at Aker Hospital, Radiological Department, except in some cases subjected to cardiac catheterization.

The radiological examination of the patient group was carried out by one person, the head of the department, and most cases were examined twice or more at intervals varying from months to years. This ensures as uniform and reliable an assessment as possible. The results used in the present study are those obtained by the radiological examination performed at the time of my own examinations.

## CHAPTER V

### The Normal Series

#### 1 Criteria for selection of normal controls

The normal series comprised 111 men whose ages ranged from 20 to 64 years. The greater part of the series — 79 persons — all of them over 30 years of age, was selected from amongst the personnel employed at two industrial concerns in Oslo or at Aker Hospital. All these persons had been examined annually by their industrial medical officer for many years, and were selected in co-operation with

him. These 79 persons were followed up a year later with clinical and electrocardiographic examination. No one had in the meantime developed signs of cardiovascular disease.

A few subjects in the normal series were patients admitted to the hospital, at the time of this investigation, for relatively innocent illnesses of non-cardiovascular origin.

The majority of the persons under the age of 30 years were medical students.

In spite of absence of a corresponding group in the patient material, a group of 22 men under the age of 30 years was included, nevertheless, in the normal material, for the purpose of evaluating the normal ballistocardiogram and changes appearing in it on ageing.

This study does not include women, chiefly because this would lead to a considerable extension of the scope of the work. The ballistocardiographic investigations would require a sufficiently large normal series of women also, in the different age groups. Further the additional difficulty arises of collecting a large enough number of women with coronary heart disease in the relevant age groups. One must also consider the problem that patients who, in addition to their cardiac disease, suffer from hypertension or overweight, are to be excluded from a ballistocardiographic investigation aiming at evaluating the particular ballistocardiographic alterations which appear in coronary heart disease.

In the normal material subjects were not included in whom cardiac disease was suspected on the basis of the anamnestic data, the clinical findings, or the electrocardiographic and radiological examination.

None of the normals had had symptoms of cerebrovascular disease or intermittent claudication, and in all cases both femoral and popliteal artery pulsation was present.

Blood pressure was normal (see criteria p. 20) and had, in the age groups over 30 years, with few exceptions been recorded annually for many years by industrial medical officers.

No signs of pulmonary disease were found by clinical and radiological examination, and all the normals had a vital capacity exceeding 2.5 litres.

There were no cases of overweight, using as a criterion a weight related to height 15 per cent in excess of the normal mean for Norwegian males (51).

## 2. PRECORDIAL PALPATION

On palpation of the precordium usually one impulse only is felt, the apical beat, and often, or very often, even this may not be palpable. In the 111 men comprising the normal material the apical beat could be located in 65 cases (60%). Table 1 shows the incidence of palpable apical impulse in various age groups and the age distribution of the material.

It will be seen as well that the apical

Table 1 Incidence of palpable apical beat in different age groups, and distribution of normal material in age groups

| Age, years        |                 | < 30 | 30-44 | 45-54 | 55-64 | Total |
|-------------------|-----------------|------|-------|-------|-------|-------|
| Number of persons |                 | 22   | 35    | 36    | 18    | 111   |
| Apical beat       | Not palpable    | 6    | 12    | 18    | 10    | 46    |
|                   | Normal          | 16   | 22    | 15    | 8     | 61    |
|                   | Heaving grade I | 0    | 1     | 3     | 0     | 4     |

mately in the middle of the pulsatory bulge which may be encountered in cases with markedly enlarged right ventricle and is usually referred to as the left sternal lift (see p. 13)

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There were no cases of overweight, using as a criterion a weight related to height 15 per cent in excess of the normal mean for Norwegian males (51).

## 2. PRECORDIAL PALPATION

On palpation of the precordium usually one impulse only is felt, the apical beat, and often or very often, even this may not be palpable. In the 111 men comprising the normal material, the apical beat could be located in 65 cases (60%). Table 1 shows the incidence of palpable apical impulse in various age groups, and the age distribution of the material.

It will be seen as well that the apical

Table 1 Incidence of palpable apical beat in different age groups, and distribution of normal material in age groups.

| Age, years        |                 | < 30 | 30-44 | 45-54 | 55-64 | Total |
|-------------------|-----------------|------|-------|-------|-------|-------|
| Number of persons |                 | 22   | 35    | 34    | 18    | 111   |
| Apical<br>beat    | Not palpable    | 6    | 12    | 18    | 10    | 46    |
|                   | Normal          | 16   | 22    | 15    | 8     | 61    |
|                   | Heaving grade I | 0    | 1     | 3     | 0     | 4     |



beat was evaluated as probably heaving in four cases, a problem discussed in more detail later

### 3 REGIONAL CARDIOGRAPHY

Registration of precordial pulsations yields a detailed tracing of impulses (propulsions and retractions) transmitted to the precordium at each cardiac thrust. Outward impulses result in positive waves, whereas retractions result in negative waves.

Nomenclature varies, and is hardly standardized yet. The letter symbols of Harrison and co-workers (Fig. 2) are used here, with some modifications. Later on in this work, the waves used in an attempt to differentiate normal from pathological, will be named according to their presumed etiology. This will be referred to in the discussion.

#### a) The more important normal waves

The typical apexcardiogram has been described by the authors referred to above, and by Luisada & Magri. The normal

variations in the apical tracing and left sternal tracing (left 5th intercostal space at the sternal border) will therefore, be the main topic of discussion here. These two points were selected, as mentioned because pathological pulsations primarily are evident here, from the left and right ventricle respectively

Both tracings often show an atrial wave — a — normally positive, form and size corresponding approximately to the P wave in the electrocardiogram (Fig. 3). It is visible more frequently and is usually slightly larger in the left sternal tracing (LST) than in the apical tracing (APT). It was visible in LST in 87 of the 111 normals (80 per cent) and in APT in 60 normals (53 per cent). It is fairly constantly related to the P wave on ECG with the peak at 0.07—0.08 seconds after the peak of the P wave (Table 2) and synchronous with the 4th heart sound in cases where the latter is visible in the phonocardiogram. The onset of waves may be difficult to determine precisely and the peak point is chosen, therefore, in the waves described. In addition, it is desirable to use the peak of waves in

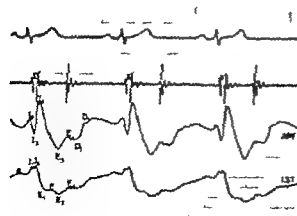


Fig 3 Reading from above downwards Electrocardiogram Second standard limb lead, phonocardiogram 23 cycles per second band, the precordial tracing (APT), and the left sternal tracing (LST)

a = atrial wave. I = waves in isometric phase of systole. I is peak of wave corresponding to pical beat. E = waves in ejection phase. D = waves during protodiastole. Ds is peak of rapid filling wave. P per speed = 30 mm/sec., each mm on the paper corresponding to 0.02 second. The same paper speed is maintained in all subsequent figures.

Table 2 Distance between peak of P wave in ECG and top of atrial wave and distance from start of QRS complex to top of  $I_2$  and  $I_4$  - graded in 1/100 sec  
Cardiac rate 44-100 average 65/min

| Measurements                   | The apical tracing | The left sternal tr. cl. g. |
|--------------------------------|--------------------|-----------------------------|
| Peak P wave - peak atrial wave | 4-9 mean 7.4       | 5-9 mean 6.7                |
| Q wave - peak $I_2$            | 4-8 mean 5.7       | 4-9 mean 6.6                |
| Q wave - peak $I_4$            | 9-17 mean 13.3     | 9-15 mean 11.5              |

doubtful cases when trying to identify a wave by its temporal relationship to ECG waves. The atrial wave is slightly earlier in LST than in APT and does not normally exceed 2-3 mm in height in the apical area, it was in no case greater than 30 per cent of the size of the total excursions in the apexcardiogram, calculated from the highest to the lowest point on the tracing.

A sharp positive wave  $I_2$  (Fig. 3) initiates systole and the beginning of the apical beat. It commences between the Q and R wave in the ECG reaching a peak approximately 0.06 seconds after start of the QRS complex and somewhat later in LST than in APT (Table 2).  $I_2$  is always small in size rarely higher than 2-3 mm, and about equal in both APT and LST. In LST however it may be slightly larger more often visible, and more impressive because the apex beat impulse is usually insignificant in this area.  $I_2$  may be very small, and was, in the normal material, present in 57 per cent only in APT and in 66 per cent in LST being absent equally frequently in younger and older subjects. Its size bore no constant relationship to the total systolic amplitude or the shape of the curve.

A more or less sharp inversion is seen

in the tracing,  $I_2$ , situated between the two positive waves  $I_3$  and  $I_4$  in the isometric phase of ventricular systole. It occurs in both APT and LST being larger more constant, and seldom entirely absent, in APT.

$I_4$  is usually the largest positive wave seen on the apexcardiogram. It has a sharp or slightly rounded peak, being situated on average 0.13 seconds after onset of QRS and corresponding to the latter part of the 1st heart sound, just following the large vibrations marking the opening of the semilunar valves (52). This wave  $I_4$  is always present in the apical area, and is most prominent corresponding to the apex beat itself. It decreases quickly in a lateral direction, and more slowly towards the median. It is usually small or minute at the left sternal margin, with the peak occurring also slightly earlier at this point (Table 2). It may however under normal circumstances be high in LST too in some thin or young subjects (Figs. 4b 7a). The form of the tracing in that case does not deviate from the apexcardiogram to any great extent. Eddleman *et al.* (26) found this type of tracing in nine out of 64 normal young men, seven of whom had a 'thin chest'. In the present series, 11 men were

found to show similar findings, one of whom had a slight degree of funnel chest, and eight were tall had a meso-ectomorph body build and a semiverical or vertical ECG axis.

Cardiac contraction during the ejection phase of systole is denoted by a deep inversion of the tracing  $I_1 E_4$  (Figs. 3-4). The further course of the tracing in this phase varies normally to some extent, showing at times a small midsystolic positive wave of doubtful significance  $E_2$ . The curve rises again evenly towards a more or less well pronounced peak,  $E_3$  corresponding to closure of the semilunar valves and end of systole.

After valve closure a new inversion is seen of the tracing, varying in depth and steepness, to point  $D_1$  which coincides with the top of the v wave in the jugular phlebogram, and with an eventually visible opening sound or opening snap. For this reason it is assumed to mark the opening of the a-v valves ( $S_2$ ).

The rapid filling wave  $D_1 D_2$  marks the first rapid filling phase of the ventricle,  $D_2$  coinciding with the 3rd heart sound, if present, or a rapid filling gallop. The rapid filling wave (RFW) was always present in the normal apexcardiogram, but varied considerably in size (2-25 mm mean 7 mm). It could be the largest wave in the tracing in some few cases with small systolic excursions or in which RFW itself was very large. The steepest rise occurs usually in its first part, flattening out towards the peak  $D_2$  often with a visible small dip.

The angle formed by this wave and the horizontal in the apical tracing has been measured — the rapid filling angle (RFA). The initial steepest part of the

wave was used in measurements in cases where the upper part of the wave flattened out. Average angle between RFW and the horizontal was found to be 50 degrees, with outer limits of 30-80 degrees. No correlation was found between size of RFA, and cardiac rate and length of diastole, or between size of RFA and total excursions in the tracing. A definite positive correlation was found, however, between the angle and absolute size of the rapid filling wave. An RFW of 10 mm or more never had an RFA below 60 degrees. An RFA below 50 degrees was found in 19 cases, none of which had an RFW exceeding 4 mm. It may be of interest to note that only two of these cases were under 45 years of age.

#### *b) Normal variations in the apical tracing*

The typical pattern in the apexcardiogram found in 71 persons was a narrow fairly well differentiated  $I_4$  reflecting the apical thrust, followed by a more or less deep inversion in the ejection phase of systole.  $I_4$  was tall or of medium height in 48 of these cases (Fig. 4) 37 of whom had a palpable apical beat. The apical beat was palpable in only 5 of the 23 cases with a small or tiny  $I_4$  and many showed a systolic complex lowered to, or below the base line (Fig. 5).

The apexcardiogram deviated in appearance to some extent in 15 cases, showing a relatively deep  $I_2$ , small  $I_4$ , and absent or slight inversion of the curve during ejection phase (Fig. 6). However, these 15 subjects did not differ from the average as regards age, body build, or electrocardiographic findings, but it was remarkable that a palpable apical beat

Fig. 4 Apical tracing, and below is the left sternal tracing, in three normal subjects. Typical normal pical tracings showing narrow rather well-developed I reflecting the pre beat, followed by the usual deep inversion during ejection phase of systole.

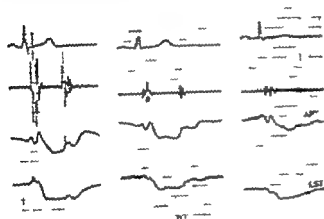
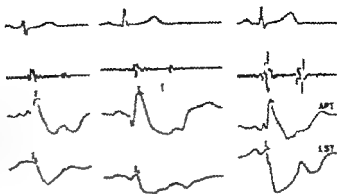
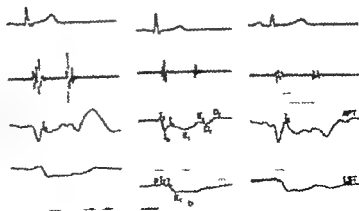


Fig. 5 Apical tracing and left sternal tracing in three normal subjects. Amplitudes are small or very small. On Fig. 5b practically the entire systolic complex is below the base line. Small amplitudes are also observed in most of the left sternal tracings.

Fig. 6 Normal pical tracing, though somewhat decreasing in appearance I is small or minute preceded by relatively deep I. Absent or very slight inversion of the tracing during systolic ejection. Small amplitudes also present in the left sternal tracing. A palpable pre beat is rarely found in person with this type of tracing.



was found in one case only. One assumes, therefore, that these cases do not represent a special group except in so far as they comprise the part of the material in which the precordial pulsations in the apical area are least marked.

However the remaining 24 subjects in the normal material can, and should, be separated as a special group because of the appearance of their apexcardiogram. This is the group which mainly gives rise to difficulties in separating the normal and pathological apexcardiogram.

The main deviation in appearance of the apexcardiogram in this group is due to *course and shape of the systolic waves*.  $I_4$  dominates the isometric phase of systole completely with a peak which is often more plump and broad than usual, frequently flattened and often slightly biphasic (Fig. 7). The preceding waves  $I_2$  and  $I_3$  are often small and appear as a small notch or indentation at the start of the rising part of  $I_4$ , especially when the latter is very prominent, or they may be entirely absent.

Peak of  $I_4$  is, as usual, followed by a rounded downward convex inversion.

However in this group the inversion rapidly flattens to a plateau lasting practically throughout systole, until a further sudden fall corresponding to, or just before, the start of the 2nd sound. This fall ends at  $D_2$ , usually the deepest point on the tracing, the start of the rapid filling wave then following.

This type of apexcardiogram differs from the usual especially as regards the late systolic plateau, following the apical thrust proper. However transition forms are encountered in which the wave in version during systolic ejection becomes so deep that it can hardly be described any longer as a plateau. On the other hand, tracings are seen where the position of the plateau is high or very high (Fig. 7). This type of tracing is the one which is difficult to differentiate from the pathological systolic plateau found in left ventricular hypertrophy all the more so because clinical evaluation of the quality of the apical beat in this group — heaving or not heaving — is sometimes very difficult.

A palpable apical beat was encountered in 22 of 24 subjects in this group, being

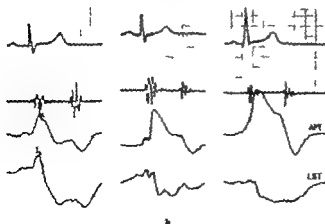


Fig. 7 Three examples of late systolic plateau in the precordial tracing.

- Relatively deep inversion during ejection phase of systole, with low-lying plateau. In addition, the left sternal tracing shows aberration in focus with a tall I.
- Plateau of medium height.
- High plateau.

often very prominent. As a rule one could be reasonably certain as to whether or not the apical beat was heaving in character by feeling the typical short thrust against the finger followed by the normal retraction during the latter part of systole. In a few cases, however the findings on palpation were doubtful especially if some degree of pressure was applied by the palpating finger or palm of the hand.

Serious doubt arose in four of the 24 cases, as to whether the apical beat was heaving or not. The apexcardiogram did not differ in form, however from the other tracings in the group but three of the four tracings showed great or very great excursions. Considering the group as a whole, all cases were below the age of 35 years. As many as 10 of them, however were in the age group 45-54 years. They were slim persons with a height relatively great in proportion to weight. Compared to the rest of the material, a larger number than usual had an ectomorphic body build, and the majority had an ECG with vertical or semivertical axis. Similar constitutional factors and ECG findings were observed in the 11 cases described previously (p. 27) in whom I was unusually tall in the left sternal tracing, resulting in a tracing resembling a normal apexcardiogram. It is relevant, too, that 6 of these cases showed a late systolic plateau wave in the apical tracing (Fig. 7a)

#### c) *The left sternal tracing*

This tracing tends to have a much more constant appearance under normal conditions than does the apical tracing. Amplitudes may vary considerably but the

tracing remains dominated, with the few exceptions mentioned previously by the deep ejection wave (Figs. 3-7).

Usually the apical wave is small or barely visible, the preceding positive wave  $I_2$  appearing relatively more predominant than in the apical tracing.

The atrial wave is somewhat more prominent and is more often visible than over the apical area. Systolic plateau waves were not observed in the left sternal tracing in the normal material.

#### 4. AUSCULTATION AND PHONOCARDIOGRAPHY

A visible 3rd heart sound (rapid filling sound) was found on phonocardiography in 11 of 31 subjects under the age of 35 years, and only in one above the age of 35. A 4th heart sound (atrial sound) was observed in four and three persons in these age groups respectively. The 3rd heart sound was heard also in some of the younger subjects, but never above the age of 35 years.

A number of difficulties are encountered in the exact determination by auscultation and phonocardiography of the relative strength of the 1st and 2nd heart sounds over the apex. The following conclusions may be drawn:

1. Apical heart sounds diminish rapidly in loudness with increasing age.
2. The 1st heart sound over the apical area is usually louder than the 2nd sound in younger people, and is usually louder or as loud as the 2nd sound in older people, though with numerous exceptions.
3. A number of extra-cardiac causes

exist of combined weakening of the 1st and 2nd sound over the precordium. In this study only those cases were recorded in which marked weakening of the first apical heart sound compared to the second sound was noted, excluding the cases in which the loudness of both sounds was reduced.

Findings in the normal material showed that it was very difficult to delineate, both on auscultation and by phonocardiography cases in which the apical 1st heart sound was weakened in proportion to the 2nd sound to an extent which could be considered pathological. Difference in pitch often causes difficulties in the auscultatory assessment of the relative strength of the two sounds. In all too many cases poor agreement was found between the phonocardiogram (aural band) and the auscultatory findings.

I therefore refrained from further evaluation of this otherwise good clinical sign.

### 5 Electrocardiography

Subjects included in the normal series all had normal ECG as regards the P wave, a-v conduction time, width and shape of QRS complex, ST course, and absolute size of T wave. Use of Sokolow & Lyon's criteria for left ventricular hypertrophy in this study implies therefore that only criteria concerning voltage are of interest and may lead to deviation from the normal.

The deviations from the normal were, in fact, practically all due to too high voltage in the precordial leads.

The height of R wave in  $V_4$  or  $V_6$

exceeded 26 mm in six cases, with values of between 26-29 mm. The sum of R in  $V_4$  and S in  $V_1$  was 35 mm or more in 13 cases, with values between 35-39 mm in nine, and between 40-45 mm in four. Both criteria just exceeded the upper limit of normal in three of these cases.

The normal material was selected on the basis of strict criteria, clinical, radiological and electrocardiographic. Practically the entire normal material was followed up personally or by contact with industrial medical officers. It is reasonable to assume, therefore, with a fair degree of certainty that the apparently pathologically high voltage found in these 19 cases represents in fact a false positive finding. Other investigators (15) have found a similar incidence of false positives on using precordial lead voltage as a criterion of left ventricular hypertrophy. This means that Sokolow & Lyon's criteria for maximal normal voltage in precordial leads must be used with great caution. At any rate, a moderate increase above the limits described must not be taken as a sign of hypertrophy unless other and more definite signs are present in addition.

The voltage of  $R_1 + S_3$  waves in the standard limb leads, and the voltage of R wave in lead aVL did not, on any occasion, exceed the conventional criteria. One case had an R wave in aVF exceeding 20 mm, but an otherwise normal ECG.

### 6 RADIOLOGICAL EXAMINATION

A relative cardiac volume exceeding 500 ml was not found in any case in the normal material. Cases with borderline vol

urines (455-500 ml) were excluded from the normal material, if there was any suspicion of the presence of heart disease on the basis of other radiological findings or other symptoms or signs, the same criteria of selection used for all normals.

Nine persons had a relative volume between 460-490 ml.

With a few exceptions all the normals, including the nine with borderline volume were examined a year later both clinically and with ECG and none had developed coronary heart disease during this period.

## 7 DISCUSSION

Many unsolved problems exist concerning the origin and possible hemodynamic significance of the numerous small or inconstant waves observed on registering precordial pulsations. Harrison and co-workers have done major work in this field (12 25 34 36 38 64, 71).

Nomenclature currently used is unwieldy but necessary in order to allow identification of various waves under normal and pathological conditions. However

understanding of the tracing and clinical application of the method will, in the author's opinion, be made easier by giving individual names to waves related to definite occurrences in the cardiac cycle, and placing them in relation to these events. This in no way prevents the use of recognized letters or figures on the waves, or parts of them, as the occasion demands.

The following may be accepted as established facts

- 1) That the a wave is due to atrial contraction, this based on the fact that it bears a constant time relationship to the P wave on ECG both in normal P-Q interval and in a v block (53). This wave is referred to hereafter as the atrial wave, or ATW (Figs. 8 and 13d)
- 2) That the wave I<sub>a</sub> is the graphical expression of the apical beat, although this wave, and the apical beat as well, may be modified by other adjacent impulses, for example the depth of subsequent retraction during ejection phase of systole. I<sub>a</sub> is termed the apical wave, or APW

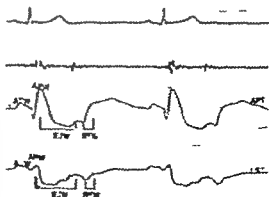


Fig. 8 The most important waves in the apical tracing, using simplified nomenclature. ATW = atrial wave. APW = apical wave. EJW = ejection wave. RFW = rapid filling wave.



- 3) That the more or less deep inversion of the curve which follows the apical wave corresponds to the ejection phase of systole (26) This entire wave is termed the ejection wave, or EJW and the symbols  $E_1$   $E_4$  will be used to denote points on or parts of the wave.
- 4) That  $D_1$   $D_2$  wave corresponds to the first rapid filling phase of diastole (52, 53) This wave is called the rapid filling wave, or RFW

The atrial wave was found to be normally small positive and similar in size and shape to the P wave in ECG. It is usually not more than 2-3 mm high when using an amplification which gives a reasonable amplitude during ventricular systole. Findings here correspond with those of Harrison and co-workers (38-85, 86) i.e. normally it is not more than 25-30 per cent of the total amplitude on the apexcardiogram, calculated from the highest to the lowest point on the tracing, and thus only exceptionally when the total amplitude is small or very small.

The apical wave, as seen on apical tracing, is a narrow positive wave, followed by the deep inversion which is called the ejection wave. These two waves are the first to be affected when precordial pulsations are small, other waves remaining relatively intact (Figs. 5-6). In the case of small excursions relatively slight difference in size and course of waves will result in apparently large variations in the appearance of the apexcardiogram. The tracing also shows some variations in appearance on repeated investigations. No definite basis is found therefore, for differentiation between certain types of tracings in these cases. The only definite

common clinical finding in this part of the normal material is that the apical beat reasonably enough is often not palpable.

Position of the systolic waves, as a whole, in relationship to the base line, also plays a part in the appearance of the apical tracing. In some cases, the entire systolic complex may be buried under the base line. In other cases it is level with it and in others again it may be entirely above the line. This is illustrated in Fig. 5 and also, in my opinion, in the diagrams of tracings from the three types described by Eddleman *et al* (26) in a normal material comprising 64 young men, and reproduced here by kind permission of the author (Fig. 9) Diagram D shows this most clearly representing superimposed records from the three types from  $V_4$  position.

The observation of Eddleman *et al* that the apical wave may be tall also along the left sternal margin (Fig. 9, type II), resulting in a tracing resembling that of the apical area, has been confirmed in the present work. Further confirmation was obtained of the observation of the same authors that this type of tracing is usually associated with a particular body build.

The findings in the apical tracing enable separation of a group comprising 22 per cent of the normal subjects. The usual inversion following the apical wave is replaced by a shallower wave than normal, which continues into a plateau of variable height in late systole, i.e. the plateau in these cases is late systolic and not pansystolic.

Lunada & Magri (53) found, as mentioned, that in a normal apexcardiogram, systole may be dominated by a plateau

wave, apparently pansystolic, according to their description.

Eddleman *et al* found no cases in which such a plateau wave occurred normally either pansystolic or late systolic. They consider the difference to be due to Lusada & Magni using elastic fixation, whereas they used a crossbar to hold the chest piece in position.

In the present study great stress was laid on fixing the microphone as rigidly as possible to a point outside the body and a metal bar was used to apply it perpendicularly towards the precordium. Height of the waves in the type of tracing referred to above may vary depending on the pressure employed to press the

microphone against the precordium, but the actual shape of curve remains unchanged. Small amplitudes were obtained on light pressure, increasing rapidly to a maximum with increasing pressure of the endpiece, remaining unchanged on further increase of pressure.

Heyman (45) used an equipment similar to that in the author's work. He investigated the effects of varying pressures on the endpiece on recording the arterial pulse. Only wave peaks were depicted on the tracing when the endpiece just reached the artery. More and more of the waves appeared as the microphone sank farther in, and the entire wave was recorded at a critical depth.

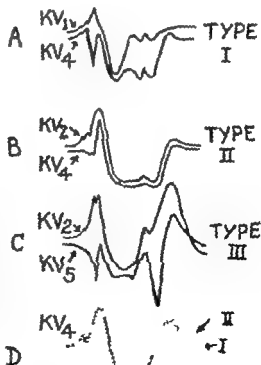


Fig 9 Three different types of tracing as found by Eddleman *et al*. Diagram B shows similarity of tracings in V and V position in type II individual. Diagram D represents superimposed record from the three types from V position. The systolic complex and its relationship to the base line is shown. Amplitudes in type III are small and practically the entire systolic complex lowered below the base line.

(From Eddleman E E J *et al* 'The Kneecardioagram II The Normal Configuration and Amplitude' *Circulation* Vol. VIII, # 373 1953 Reproduced by permission of the American Heart Association and the author)

The course of the tracing obtained in this group with late systolic plateau, moreover corresponds well with findings on palpation in the group. There can be no doubt that the tracings reproduce pulsations as they are felt by careful palpation. Clinically the group is important because of difficulty in separating the plateau wave obtained from that to be found in pathological conditions. This is even more relevant in these cases, in which one often runs into difficulties on clinical examination, when trying to determine whether or not the apical beat is heaving in character.

The apical beat is nearly always palpable and often prominent in these cases and may be felt during most of systole. As a group these subjects tend to have great body height in proportion to weight, are frequently of the ectomorph body type, and with a vertical or semivertical ECG axis. The aberrant form of the apical tracing, and to some extent of the left sternal tracing in this group, can, in all probability be accounted for by body build, intrathoracic position of the heart and intrathoracic space proportions, or compressibility of the chest wall.

The most reasonable explanation is that the microphone used, in common with the palpating finger is applied to the precordium, exerting a certain amount of pressure, and will thereby come into closer contact than usual with the heart via the chest during the entire systole.

It is worth bearing in mind that apex cardiograms with a high late systolic plateau may be obtained in cases with resected ribs, or following operative treatment of a left breast cancer where the thoracic wall is thin and weak. This finding has

been observed in two cases not included in this material. Reports in the literature suggest that this will be the usual type of tracing when the examination is performed in the left lateral position (1: 66).

The rapid filling wave (RFW) in the apical tracing and the angle  $\alpha$  forms with the horizontal — the rapid filling angle (RFA) — have attracted attention, in relation to functional diagnosis of mitral stenosis. The assumption is that a somewhat pronounced narrowing of the mitral ostium will influence the size and gradient of the rapid filling wave.

Benchimol *et al* (1960) investigated this point. Apexcardiograms were recorded with the subjects lying on the left side, in a patient group and in 40 normal controls. All the controls had an RFW with RFA varying from 32 to 77 degrees (average 54 degrees).

In my normal series, an RFW was also recorded in all cases, though with considerable variation in size (2.25 mm, mean 7 mm) and with an RFA of 30–80 degrees, mean 50 degrees. A definite positive correlation was found between height of wave and size of angle. RFA was less than 30 degrees in 19 cases, none of which had an RFW exceeding 4 mm, and the RFA in cases with RFW of 10 mm or more was never less than 60 degrees.

As long as absolute size of the rapid filling wave varies to some extent according to pressure on the chest piece, and reliable calibration is not available, figures given will, of course, have only a limited value. It is obvious too, that size of rapid filling angle depends on the speed of recording paper which was 50 mm per second in this study as in that of Benchimol *et al*.

## 1 SUMMARY OF CHAPTER V

The criteria for selection of the normal controls are described. A short account of palpation findings in the different age groups is followed by a description of the more important waves seen in the apical tracing and their normal variations. Findings in the normal material are used as a basis for the differentiation between the normal and pathological. Criteria for this differentiation are given in Chapter VI in connection with diagnosis of the parasternal plateau.

After a short description of the normal appearance of the left sternal tracing, Chapter V continues with an account of phonocardiographic findings in the normal material. A visible 3rd heart sound (rapid filling sound) occurred frequently in the age group below 35 years, but was present in one person only above that age, whereas a visible 4th heart sound (atrial sound) was found in three persons above the age of 35.

At the electrocardiographic investigation cases were included in the normal material only if ECG was normal as regards P wave, a-v conduction time, width and shape of QRS complex, course of ST segment, and absolute size of T wave. Use of Sokolow & Lyon's criteria for left ventricular hypertrophy in this study implies therefore, that only criteria concerning voltage may lead to deviation from the normal.

A total of 19 persons of 111 (17 per cent) were found with an P wave in  $V_4$  or  $V_6$  exceeding 16 millimetres, or where sum of R in  $V_3$  and S in  $V_1$  was 35 millimetres or more.

Similar findings are made by Cournand & Proudman (1959) and one cautions, therefore, against considering a moderate increase above the norm as a sign of left ventricular hypertrophy unless other more definite signs are present in addition. No case of abnormal voltage in the standard limb leads was found, and one case only showed an R wave in aVF exceeding 10 millimetres, the ECG in other respects being normal.

Finally in Chapter V normal variations in the apical tracing, and left sternal tracing are discussed, as are results which deviate from those in previous investigations.

The most important deviation from the norm was found in a group of 14 persons (22 per cent) whose apexcardiogram showed a more or less high late systolic plateau instead of the usual deep inversion of the wave in the ejection phase of systole. This group has a prominent apical thrust, considerable doublet existing in some cases as to whether it was in fact, heaving in character.

Reliability of the observations made is discussed.

only if the height of plateau above lowest point on the tracing exceeded 80 per cent of the total excursions. Forty tracings with late systolic plateau wave and 26 pansystolic were found in the entire patient material using these criteria. Diagnosis was uncertain in eight cases.

In addition comes group III discussed later including 13 definite and two doubtful cases with pansystolic plateau wave in the parasternal area.

Patients were not, in this connection, divided into age groups or groups with and without hypertension. Tracings ob-

tained from hypertensive persons did not deviate to any appreciable extent from the rest of the material. Two smaller groups were, however, divided off from the main group on the following lines:

Group I Main group 139 patients with coronary heart disease and normal weight, according to previously stated criteria.

Group II Overweight patients. These 30 cases were placed in a subgroup in order to determine the effect, if any of obesity on reliability of regional cardiography.

Fig. 12. The apical tracing shows a pansystolic plateau tracing following a small initial peak, it rises evenly throughout the entire systolic ejection phase. Fig. 12a shows pansystolic plateau present in the left sternal tracing as well.

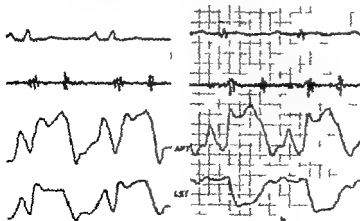
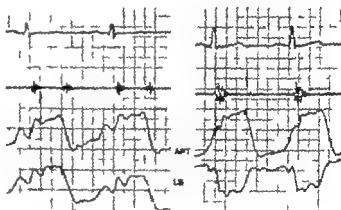


Fig. 13. Pansystolic plateau in the apical tracing, showing rise towards the end of systole for a transient fall following peak of the apical wave.

Atrial wave shows pathological enlargement, and 4th heart sound is visible. Rapid filling wave is short and steep.

Group III 13 patients, all with a localized heaving impulse in a limited area around the parasternal line about half way between the apical area and left sternal border

## 2. CLINICAL EXAMINATION AND REGIONAL CARDIOGRAPHY

### a) Results in group I

Table 3 illustrates results in this group. The apical beat is usually not palpable in cases with small or very small excursions in the apical tracing.

Of greater interest is the finding of a probable heaving apical beat in as many as 10 out of 36 patients with a late systolic plateau. The apical beat is usually palpable and often prominent in these cases, and assessment of palpation

findings is difficult enough in a normal material as mentioned, and becomes even more so when the examiner is fully aware of the presence of known heart disease.

Comparison of the apexcardiogram and the radiological findings, meanwhile, support the finding in the normal material that a late systolic plateau wave is a normal phenomenon and shows that the apexcardiogram may correct effectively a doubtful palpation finding.

Pansystolic plateau in the apical tracing was found in 22 cases in this group. On palpation the apical beat was definitely heaving in four cases only whilst as many as 15 were registered as probably heaving. Here too the radiological findings showed conclusively that pansystolic plateau waves are pathological. Further

Table 3 Group I Relationship between apical tracing and clinical phonocardiographic and X-ray findings

| Apical tracing                           | No. cases | The apical beat |              |         |          | Phonocardiography |                    |                      | Roentgen volume           |             |            | Atrial wave |
|--|-----------|-----------------|--------------|---------|----------|-------------------|--------------------|----------------------|---------------------------|-------------|------------|-------------|
|  |           | Normal          | Not palpable | Heaving |          | Third heart sound | Fourth heart sound | Third + fourth sound | 450-500 ml/m <sup>2</sup> | 45-500 ml/m | > 500 ml/m | Pathologic  |
|  |           |                 |              | grade I | grade II |                   |                    |                      |                           |             |            |             |
| Normal (asynchronous or high excursions) | 29        | 1               | 7            | 1       | 0        | 0                 | 3                  | 0                    | 24                        | 2           | 3          | 1           |
| Normal (small excursions)                | 46        | 10              | 35           | 1       | 0        | 0                 | 2                  | 0                    | 34                        | 9           | 2          | 1           |
| Late systolic plateau                    | 34        | 21              | 5            | 10      | 0        | 0                 | 0                  | 0                    | 32                        | 3           | 1          | 0           |
| Pansystolic plateau                      | 22        | 0               | 3            | 15      | 4        | 2                 | 11                 | 3                    | 3                         | 5           | 14         | 11          |
| Pansystolic plateau?                     | 6         | 2               | 0            | 4       | 0        | 0                 | 1                  | 0                    | 4                         | 1           | 1          | 0           |

support was obtained by the fact that a 3rd and/or 4th heart sound was recorded in 16 of these 22 cases (Table 3). A registrable 3rd or 4th heart sound, by the method used and in the age groups involved, should be a rather reliable sign of diastolic gallop judged by findings in the normal material.

Atrial waves in the normal material never exceeded 30 per cent of total excursions in the apical tracing. Using this criterion, a pathologically enlarged atrial wave was present in 13 cases in group I. Eleven of these patients also had a pansystolic plateau wave and 10 a recordable 3rd and/or 4th heart sound. Relative cardiac volume varied from 440-740 ml, mean 560 ml. It is worth mentioning that the patient with a cardiac volume of 440 ml had, in fact, pulsus alternans and an audible presystolic gallop at the time of the examination, and he developed later a difficult tractable left ventricular failure.

It follows from the findings referred to above that a pathological atrial wave may be found in the apexcardiogram

without an accompanying pansystolic plateau wave. In the whole material four such cases were found (Fig. 14). Their relative cardiac volume was 470-560 ml, mean 510 ml. The 4th heart sound was visible in three cases and two showed signs of incipient cardiac failure. The apical beat was not palpable in any of the four cases. One of the two patients who showed signs of failure subsequently died.

A pathological atrial wave, even as an isolated finding, appears to be a reliable indicator of an enlarged and probably failing heart.

A pansystolic plateau wave in the left sternal tracing was found in five cases in group I (Figs 11a, 12a, 13a). All five had apical pansystolic plateau wave too, and all but one showed pathological atrial wave. Visible 3rd and/or 4th heart sounds were found in four cases. All five showed signs of cardiac failure, and three of them have subsequently died. Radiological examination showed cardiac enlargement in these cases, relative volume being 540-690 ml, mean 610. The

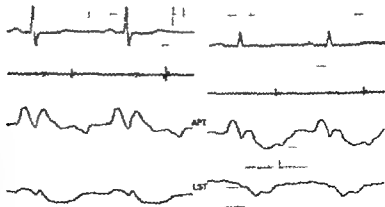


Fig 14 Two cases showing pathologically enlarged atrial wave in the apical tracing, the only positive finding.

radiological examination stated that either left-sided or overall enlargement was present.

Table 3 shows that three of the cases with pansystolic apical plateau wave had a heart volume within normal limits, whereas the volume was borderline in five cases. However all the three patients whose cardiac volume was within normal limits had recently been treated for definite cardiac failure, or developed failure within a short time. An audible presystolic gallop and pathological atrial wave were present in one case. The two others died later from their heart disease. Two of the five cases with borderline heart volume developed cardiac failure a short time after the examination, and the other three had a visible 3rd and/or 4th heart sound. Audible gallop was present in one case, another had a pathological atrial wave. Three of these five cases have subsequently died. Average relative cardiac volume was 490 ml in these five cases.

Thus all cases in the group with pansystolic apical plateau show other signs confirming the pathological nature of this wave. The plateau was not observed in normal cases either and can be presumed to have the same significance as a definitely demonstrable heaving apical beat. In addition, demonstration of a pathologically enlarged atrial wave appears to be a sign of commencing or manifest cardiac failure, whilst a pansystolic plateau at the left sternal margin is assumed to be a sign of hypertrophy and enlargement of the right ventricle.

Right cardiac catheterization was performed in 23 patients for purposes not

connected with this work, using a technique described earlier (59).

Results of regional cardiography and radiological examination were compared with resting pressures in the lesser circulation. Interest was centred mainly on the relationship between 1) the pulmonary capillary wedge pressure and right atrial pressure and a pathological atrial wave, 2) the pulmonary capillary wedge pressure and a pansystolic plateau in the apical tracing, and 3) the right heart or pulmonary artery pressure and a pansystolic plateau in the left sternal tracing.

All the three above-mentioned methods yielded normal results in 15 cases, and in a further three cases a doubtful degree of cardiac enlargement on radiological examination was the only positive finding. Results in the remaining few cases do not permit one to draw conclusions as to the possible relationship between pressures in the lesser circulation and the findings on regional cardiography.

Results of my other investigations do suggest, however, that in patients with coronary heart disease and normal weight a positive finding in the apical tracing — pansystolic plateau and/or pathological atrial wave — is a highly reliable sign of cardiac hypertrophy, cardiac enlargement, and possibly commencing cardiac failure. Of the 23 group I patients with a pansystolic plateau over the apex region, 17 had, or developed, signs of manifest left ventricular failure, and 10 later died of cardiac disease.

Absence of the above-mentioned positive findings on the apexcardiogram is not necessarily a reliable indicator that cardiac hypertrophy or failure is not present.



There is evidence, however that absence of positive findings may be a good help in the prognostic evaluation.

Four cases with a relative cardiac volume exceeding 500 ml were found in the group with normal apexcardiogram (Table 3) the two cases with pathological atrial waves not included. A total of 14 cases were found with a borderline volume. One of the cases with relative heart volume over 500 ml also showed signs of left ventricular failure at the time of examination, i.e. a definite false negative finding. Signs of cardiac failure developed later however in only one of the remaining 17 cases.

A doubtful pansystolic plateau was found in the apical tracing of six group I patients (Table 3). A definite decision was difficult, as the plateau height was borderline and the wave shape somewhere between that of late systolic and pansystolic plateau (Fig. 15). Eight such cases were found in the entire material and are presumably mostly patients with a commencing left ventricular hypertrophy but one cannot exclude the possibility that some of the tracings may

represent a variation of the normal. Tables 3 and 4 show the radiological findings in this small group. None showed signs of cardiac failure at the time of examination and none developed it later. One of the patients with a heart volume within the normal limits at the time of study later died of his heart disease, the remainder surviving.

## b) Results in group II

Results of apexcardiography in overweight patients seem to be considerably less reliable as shown in Table 4. The frequency of unpalpable apical beats, as well as of small excursions in the cardiogram is, as expected, high. Phonocardiographic findings are scant, and apexcardiogram and radiological findings correspond to a much poorer extent than in group I.

The group is small and, as also shown in Table 4, figures are very small, and relatively many of the patients show doubtful borderline volume on radiograph.

With due reservation as regards these

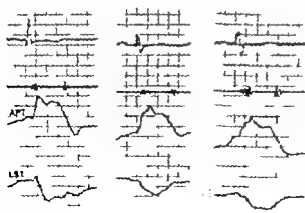


Fig. 15 Three cases showing doubtful pansystolic plateau in the precordial tracing. Height of plateau during latter part of systole is on borderline of normal, and its shape is in between that of a late systolic and pansystolic plateau. Left sternal tracing is normal.

Table 4 Group II Relationship between apical tracing and localized phonocardiography and X-ray finding

| Apical tracing                     | No. of cases | The apical beat |              |         |          | Phonocardiography |                    |                      | Roentgen volume              |                           |              | Atrial wave |
|------------------------------------|--------------|-----------------|--------------|---------|----------|-------------------|--------------------|----------------------|------------------------------|---------------------------|--------------|-------------|
|                                    |              | Normal          | New palpable | Heaving |          | Third heart sound | Fourth heart sound | Third + fourth sound | $\leq 450$ ml/m <sup>2</sup> | 455-500 ml/m <sup>2</sup> | $> 500$ ml/m | Pathologic  |
|                                    |              |                 |              | grade I | grade II |                   |                    |                      |                              |                           |              |             |
| Normal (medium or high excursions) | 3            | 2               | 3            | 0       | 0        | 0                 | 0                  | 0                    | 3                            | 1                         | 1            | 0           |
| Normal (small excursions)          | 15           | 1               | 14           | 0       | 0        | 0                 | 0                  | 0                    | 1                            | 2                         | 3            | 1           |
| Late systolic plateau              | 4            | 1               | 2            | 1       | 0        | 1                 | 0                  | 0                    | 1                            | 2                         | 1            | 1           |
| Pansystolic plateau                | 4            |                 | 1            | 1       | 2        | 2                 | 0                  | 0                    | 0                            | 2                         | 2            | 0           |
| Pansystolic plateau                |              | 1               | 0            | 1       | 0        |                   |                    | 0                    | 1                            | 1                         | 0            | 0           |

factors of uncertainty I find that apex cardiography in obese patients is considerably more reliable than clinical examination. Only five of the total of 24 patients with absent pansystolic plateau in the apexcardiogram had a relative cardiac volume above 500 ml, and two of these had a pathologically enlarged atrial wave. One of the two died later of cardiac failure. The remaining four survive and show no signs of cardiac failure.

### c) Results in group III

A few cases were found, on precordial palpation, with a limited heaving impulse midway between the apex region and left sternal border i.e. in the area around the parasternal line. This impulse was not the

apical beat, which could in some instances be palpated separately from the parasternal impulse, and was not the diffuse heaving impulse which may be found over the entire left precordium in cases with considerable left ventricular hypertrophy and enlargement. The impulse differed in localization and extension also from the so-called left sternal lift, palpable in cases with right ventricular hypertrophy.

Systematic examination of the entire patient material revealed 15 cases with this type of localized heaving impulse. A definite pansystolic plateau tracing was found in 13 cases in recordings at the point of maximum thrust (Figs. 16-17) the remaining two cases showing a doubtful plateau.

There are good reasons to believe that

these cases demonstrate sequelae of a former anterior infarction. Clinical and electrocardiographic verification of extensive anterior infarction were present except in one patient who had had a posterior infarction. All but one case were followed up for at least 1 1/2 years with ECG control. The ECG changes were persistent. The following ECG findings are common to this group.

Signs of a large anterior or anteroseptal infarction are present, with persistent QS pattern or deep Q waves over a large area

of the precordium, least changes being evident lateral to V<sub>4</sub>.

Slight to moderate persistent elevations of ST segment in several leads are also found. The elevation is usually horizontal most pronounced in V<sub>2</sub> V<sub>4</sub> and combined with a diphasic or slight to moderately inverted coronary T (Fig. 18). Such a post-infarction elevation of the ST segment when prominent is considered to be a good criterion for the diagnosis of cardiac aneurysm (3 3 83). ST elevation of the order of more than three

Fig. 16. Two of the patients with pansystolic plateau tracing, corresponding to localized midprecordial heaving impulse around the parasternal line. Rapid filling wave is very small and flat, and left sternal tracing normal

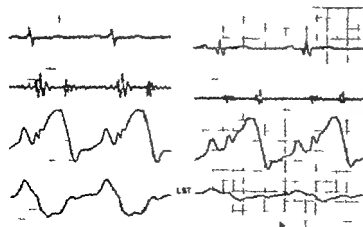
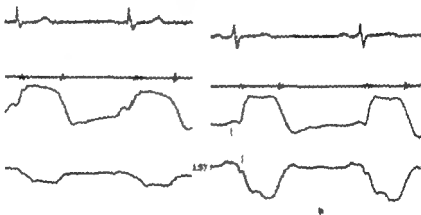


Fig. 17. Pansystolic plateau tracings in parasternal region as in Fig. 16, but showing rise towards end of systole after a tubi top of apical wave and with pathological atrial wave and small, steep, rapid filling wave.

millimetres was observed in three patients in this group, one of whom had a large anterior wall aneurysm confirmed by radiological examination. No elevation was observed in the patient with posterior infarction, and in one case with combined posterior and anterior infarction. The other cases showed ST elevations ranging from one to three millimetres. The constant appearance of this ST elevation with the two easily explicable exceptions mentioned, is a striking finding in this particular small group with its unusual precordial pulsations.

The patient series included 81 persons who had had a definite anterior infarction, but only a further eight cases showed ST changes in the precordial leads as described above.

The abnormal pulsations in the mid precordium in these patients are clearly a result of their former extensive anterior infarction. It is reasonable to assume that an area of the cardiac muscle on the anterior wall, weakened and partly fibrous, is thrown forward at each systole. The chest wall will at this point provide

an effective support for the weakened heart muscle.

Normal heart size was found in 8 of these 13 cases, using previously stated criteria, and borderline volumes in three one of whom had a pathological atrial wave. Four cases had a relative cardiac volume exceeding 500 ml two of whom showed a pathological atrial wave and three had, on phonocardiography a presystolic or protodiastolic gallop sound.

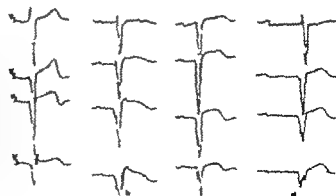
Electrocardiography was performed in eight cases in this group to detect possible paradoxical pulsations over the anterior wall. Diagnosis was confirmed in the case of the radiologically verified aneurysm mentioned above but only in a further two cases were doubtful pathological pulsations over the left ventricular wall obtained, which did not permit definite conclusions to be drawn.

#### d) Prognostic investigations

Apart from the 13 cases in which cardiac catheterization was performed, all the patients have been followed up by the

Fig. III. Electrocardiographic leads V<sub>1</sub>–V<sub>6</sub> in four of the patients with localized abnormal pulsations in area between apex and left renal border.

Q waves are deep and slight to moderate usually horizontal elevation of ST occurs constantly more prominently in V<sub>1</sub>–V<sub>4</sub>.



*Table 3 Incidence of cardiac failure and mortality in entire patient series related to findings in apical tracing Included for purposes of comparison X-ray results and frequency of audible 3rd and/or 4th heart sound in fatal cases or in those with cardiac failure*

| The apical tracing     | Number of cases | Died of heart failure | Died without heart failure | Alive with heart failure | Roentgen volume $\leq 450$ ml/m <sup>2</sup> | Roentgen volume 450-500 ml/m <sup>2</sup> | Roentgen volume $> 500$ ml/m <sup>2</sup> | Third heart sound | Fourth heart sound | Third and fourth heart sound |
|------------------------|-----------------|-----------------------|----------------------------|--------------------------|--|---|---|-------------------|--------------------|------------------------------|
| Normal tracing         | 131             | 0                     | 6                          | 1                        | 5  | 0   | 2   | 0                 | 0                  | 0                            |
| Pansystolic plateau    | 26              | 11                    | 1                          | 9                        | 3  | 5   | 13  | 2                 | 11                 | 3                            |
| Pansystolic plateau?   | 8               | 0                     | 1                          | 0                        | 1  | 0   | 0   | 0                 | 0                  | 0                            |
| Pathologic atrial wave | 4               | 1                     | 1                          | 1                        | 0  | 1   | 2   | 0                 | 1                  | 0                            |
| Parasternal plateau    | 15              | 1                     | 1                          | 1                        | 0  | 0   | 3   | 0                 | 2                  | 0                            |

rather himself with regular controls the entire time for the examination to the completion of this study or until their death. Information on the cardiac catheterization group was collected from other sources. The observation time for the patients who survived was 14-48 months, average 28 months. Four death occurred from noncardiac causes. The remaining 23 died of cardiac failure or repeated infarction, or sudden death supervened. Hypertension was present in ten of the cases who died of their cardiac disease, mild or labile in five cases, severe or permanent in the remaining five.

Table 5 shows mortality and incidence of cardiac failure in the entire material, as well as radiological findings in cases with cardiac failure and/or death.

Cases with cardiac failure tend to be concentrated in the group in which a pansystolic plateau was found in the apical region. The majority of patients who had, or developed, cardiac failure, and half of the deceased, were found in this group in spite of its representing a small part of the material only. Twenty

of the 26 cases with an apical pansystolic plateau developed cardiac failure and 12 died. One sees that prognosis appears to be poor also in the few cases showing a pathological atrial wave as an isolated finding.

These findings contrast with results in the group of 131 cases with normal apex cardiogram, where mortality was strikingly low and death occurred without preceding cardiac failure.

The group with pansystolic parasternal plateau also includes the two with doubtful parasternal plateau. It is seen that localized heaving impulse and pansystolic plateau wave in this area apparently do not have the same serious prognostic and functional consequences as the corresponding plateau wave in the apical area. In this group too a pathological atrial wave appears to imply serious prognostic consequences. In the group three cases with pathological atrial wave were found, of whom one later developed manifest cardiac failure and one died with no signs of failure. The relative cardiac volume exceeded 500 ml in both the last mentioned cases.

### 3 PHONOCARDIOGRAPHIC FINDINGS

A 3rd heart sound, 4th heart sound, or both, was recorded in 28 cases in the patient material. A total of 19 of these fall into the above-mentioned group who developed cardiac failure, or died, or both (Table 5). One case only of the 19 escaped cardiac failure and 10 of the 19 later deceased.

### 4. ELECTROCARDIOGRAPHIC FINDINGS

Sokolow & Lyon's criteria used in this study are based for the main part 1) on a voltage increase in the standard limb leads, unipolar limb leads, and the precordial leads, following a more closely defined pattern 2) on changes in ST T section in the same three lead groups. Experience obtained from normal material, agreeing with findings in a previous investigation<sup>12</sup> indicates that isolated use of voltage as a criterion of left ventri-

cular hypertrophy is not very reliable and gives many false positive findings.

Results of the electrocardiographic examination in the entire patient material, 184 cases, are presented in Table 6. Pathologically high voltage in the actual precordial leads was present in 46 patients, 26 of whom had a relative cardiac volume not exceeding 450 ml. Results in the few cases with pathologically high voltage in standard leads or unipolar limb leads seem equally unreliable.

Comparison with the radiological findings was undertaken also in cases showing depression of ST segment or T wave inversion in both standard leads, unipolar limb leads, and precordial leads. These criteria too do not correspond well with the radiological findings. Frequency of cases with positive findings will decrease considerably if one requires the presence of abnormal voltage in addition to the ST T deviations mentioned, and the majority of patients fulfilling these criteria

Table 6. Incidence of electrocardiographic findings indicative of left ventricular hypertrophy - abnormal voltage and/or multiple ST T deviation - in the entire patient series, and correlation with radiological findings

| Electrocardiographic findings                     | Number of cases | Relative volume $\leq 450$ ml/m | Relative volume 455-500 ml/m | Relative volume $> 500$ ml/m |
|---|-----------------|---------------------------------|------------------------------|------------------------------|
| Abnormal voltage precordial leads                 | 46              | 26                              | 8                            | 12                           |
| Abnormal voltage standard and unipolar limb leads | 7               | 4                               | 2                            | 1                            |
| Abnormal ST T deviations                          | 29              | 16                              | 4                            | 9                            |
| Abnormal voltage + ST T deviations                | 13              | 4                               | 1                            | 8                            |

will have cardiac enlargement at the same time.

ECG will often corroborate a diagnosis of left ventricular hypertrophy using the last mentioned strict combination of criteria. However the patient material as a whole includes 32 cases where the radiological examination revealed a relative volume exceeding 500 ml, and 31 cases with borderline volume. The small group of 13 cases with simultaneous abnormal voltage and ST T changes represents, therefore, evidently only a small number of patients with actual left ventricular hypertrophy especially as fairly definite cardiac enlargement was present in eight of the 13 cases only.

Ischemic heart disease in itself will of necessity often or very often result in ST T deviations of the same character as the ones used as criteria for the presence of left ventricular hypertrophy. The value of these ST T alterations in the diagnosis of left ventricular hypertrophy therefore, will be considerably reduced when coronary heart disease is present.

Digitalis therapy is another important factor in this respect. The criteria referring to ST T deviation are rendered useless if the patient is receiving digitalis as long as the digitalis-induced alterations cannot be clearly separated from those due to hypertrophy. It is often the case, and in this series too, that not only patients presenting evidence of heart failure will have received digitalis therapy. At some time or other such therapy may have been instituted on detecting radiological cardiac enlargement to some degree, or for other reasons, and the treatment will in these instances, usually be continued.

On the basis of experiences in the normal and patient material the conclusion is drawn that far too many false positive findings are obtained on using Sokolow & Lyon's voltage criteria for left ventricular hypertrophy. Further in this material, a large number of patients show ST T changes similar to those described by Sokolow & Lyon, but of different etiology. These criteria are, therefore, not very useful as signs of left ventricular hypertrophy in patients with ischemic heart disease.

This matter may however be quite different in a patient series comprising hypertensive heart disease. The present series includes only 34 patients with high blood pressure, the hypertension being labile in 20 of them.

Finally it may be mentioned that four cases of bundle branch block were found in the entire material. Apart from these cases, the width of the QRS complex in no instance exceeded 0.10 seconds and none had delayed onset of intrinsoid deflection, 0.06 seconds or more in  $V_4$  or  $V_6$ .

## 5 DISCUSSION

In this study clinical determination of the presence of left ventricular hypertrophy or enlargement has proved difficult.

A definite heaving apical beat could be felt only in a minority of cases, the diagnosis being very frequently more or less doubtful. Uncertainty in assessing the character of the apical beat by palpation thus occurs far too often. Further in some few cases the apical beat was not palpable or could not be localized, in

spite of the fact that a pansystolic plateau tracing was recorded at the apical region (Tables 3 and 4).

The definite existence of cardiac enlargement was even more difficult to decide by clinical examination. Definite cardiac enlargement was found in six patients, and probable enlargement in seven, using the earlier mentioned criteria laid down by Lewis (1946) the group with parasternal heaving impulse not included. This is only about half the number of cases showing fairly definite cardiac enlargement by radiological examination, but, on the other hand, radiologically verified, and usually considerable, cardiac enlargement was present in nearly all cases in this small group.

A relatively considerable cardiac enlargement was present in some of these 13 patients, in spite of the fact that the apical beat was only just slightly lateral to the midclavicular line. A few other cases had definite radiological signs of cardiac enlargement, though the apical beat was found on the border of or within the midclavicular line. On the whole, a poorer correlation was found between size of apical beat and cardiac size as judged by the radiological findings, as compared to results usual in other types of heart disease, for example, certain valvular diseases and hypertensive heart disease. A possible explanation in some cases may be that the thrust felt on palpation is due to systolic expansion of an infarcted and fibrously transformed area of the anterior wall, median to the apex, and not to the actual apex beat, a question to be discussed later on. Worth mentioning is the fact that nine of the 13 patients with clinically probable or

definite cardiac enlargement had, in fact, had a definite anterior cardiac infarction, mostly anterolateral or lateral. Three of the remaining four cases had had a posterior infarction.

As regards regional cardiography this study concentrated on differentiation of the normal and pathological apexcardiogram. With the method and criteria employed results usable in the diagnosis and prognostic evaluation have been obtained.

The significance of a pathologically enlarged atrial wave found most often in conjunction with cardiac failure, has been confirmed, agreeing with results obtained by Harrison and co-workers (35, 34, 35). According to Skinner's investigations the height of the pathological wave decreases and may be normal on instituting digitalis treatment for the cardiac failure (34).

The ability to make the decision as to whether a pansystolic plateau is present is much more important than the detection of minor variations in an otherwise definitely established plateau tracing. But even such variations may be of importance. The pansystolic wave in this study was seen to vary in appearance to some degree. A comprehensive investigation on a larger scale might conceivably reveal whether variations in the tracings (Figs. 11, 12, and 13) reflect differences in pathogenesis. The shape of the tracing may partly be due directly to the infarction itself and not to the cardiac hypertrophy present. This is true especially of plateau tracings from the parasternal region, but is probably also true of some apical tracings. This assumption is supported by recent demonstration, in cases of coronary occlusion of pathologi-



cal pulsations of the ischemic area of the heart.

Development of a cardiac aneurysm following a major infarction is a well known possibility. A larger or smaller area of the ventricular wall becomes thin and fibrous, dilating with each systole and gradually becomes distended into a pouchlike extension of the cardiac cavity (3). Scattered reports refer to more or less definite clinical diagnostic signs, a more or less widespread, though localized, heaving pulsation distinctly apart from the apical beat being the most important (14, 20, 22, 23, 67, 83).

Less well known is the frequent occurrence of systolic expansion or so-called paradoxical pulsation in the ischemic area of cardiac muscle, following coronary artery occlusion. This has been demonstrated in animal experiments, the coronary arteries being ligated (72, 101). The balloonlike propulsion in systole of ischemic cardiac muscle may be transient or remain as a permanent phenomenon. Prinzmetal *et al* (1949) found that ligation of the coronary artery near its orifice resulted in such ballooning as a constant phenomenon, and that the affected area could show marked ballooning throughout systole or early systolic contraction would be followed by late systolic ballooning of the ischemic region.

Corresponding observations were obtained on systematic studies of patients during the acute stage of cardiac infarction, using radiological techniques fluoroscopy roentgenkymography and electrokymography (16, 31, 33, 72, 97). The pathological pulsations may disappear again within weeks, or remain as permanent phenomena.

Publications in the literature about the findings on precordial palpation during the acute stage of infarction in humans are scarce (24, 46, 96, 98, 103).

Clinical findings in established cardiac aneurysm have received more attention, despite the fact that, in a not inconsiderable percentage of cases of infarction, more or less easily palpable abnormal pulsations may be felt over the left precordium, obvious to any clinician who has been engaged in these problems. Difficulties in objective recording of these pulsations probably account for this lack of interest.

Vakil (1956) found abnormal pulsations in 11 of 193 cases (5.7 per cent) during the acute stage of cardiac infarction, appearing mostly within the first week of illness and localized median and somewhat proximal to the apical area, with or without a palpable apical beat being present. The abnormal impulse was transient in nine cases, and permanent, with development of myocardial aneurysm, in two cases. Electrocardiographic findings showed widespread anterior or anteroseptal infarction.

Vakil does not explain how he differentiated between a paradoxical pulsation near the apex, and a somewhat medially situated heaving apical beat in cases where one pulsation only was palpable. However his experiences, and those of others, suggest at any rate that circumscribed expansile precordial pulsations apart from the apex, without an actual cardiac aneurysm, are a relatively frequent finding. This finding makes the clinical diagnosis of cardiac aneurysm even more difficult. Very widespread pathological pulsations indicate the prob-

ability of an aneurysm being present, and not simply a weakened area of myocardium. The majority of reports describing clinically diagnosable cardiac aneurysms are obviously based mainly on the finding of such widespread pathological pulsations (20, 22, 23, 67). Despite this, radiological confirmation of the diagnosis has been possible in about half the number of cases only (12).

Harrison *et al* (35, 37, 40, 85) used kinetocardiography to demonstrate transient paradoxical pulsations over the precordium manifesting themselves during angina pectoris, either spontaneously or when induced by activity. Suh & Eddleman (1959) demonstrated abnormal systolic outward movements or "bulges" during the acute stage of cardiac infarction in all cases in a group of 41 men by using multiple registrations over the precordium and upper abdomen just below the costal margin. Pulsations persisted in 33 patients throughout the period of hospitalization and were palpable in as many as 30 cases.

It would appear therefore that pathological pulsations, during the acute stage of infarction, are relatively common. My findings indicate that they also relatively often persist and become permanent. At least 13 of the 184 patients with coronary heart disease in my material had a persistent heaving pulsation in the mid-precordial area. None of the patients had angina pectoris during the examination. Findings remained unchanged on repeated examination, once or more, at intervals of months or years. Like Vakil's patients these cases too had extensive anterior or anteroapical infarctions. Left ventricular aneurysm was found in one case only

and only two of the 13 cases showed signs of manifest cardiac failure.

Similar abnormal impulses, transient or permanent, as a result of infarction, no doubt occur also in the lateral part of the precordium near the apex, but are in that event much more difficult to differentiate from a heaving apical impulse.

In the above the rapid filling wave has not been discussed. In the part of the patient series where the apexcardiogram was normal, it was found not to differ in appearance from the corresponding wave in the normal material. Patients in my series with both a pansystolic plateau in the apical tracing and a pathological atrial wave nearly always showed a steep and usually small rapid filling wave (Figs. 13, 17). A small rapid filling wave was also described by Skinner (1961) in patients with cardiac failure. A rapid filling wave with steep slope and of short duration was found by Warren *et al* (1958) in patients with protodiastolic gallop. Electrokymographic investigations confirm that the rapid filling period is brief in cases of congestive heart failure (Heyer *et al* 1952). Skinner's claim that the small steep rapid filling wave results from failure with subsequent increase in residual volume is in all probability correct.

Patients in my material with a pansystolic plateau but, unlike the previous group with a normal atrial wave, had a distinctly small flat, rapid filling wave (Figs. 11b, 12b, 16) which was occasionally completely absent. The fact that this pattern was also found in an unpressured number of the patients who had a pansystolic plateau in the parasternal area may be significant. On radiological

examination, cardiac volume was within normal limits in the majority of these cases.

At any rate the finding of a steep and often small rapid filling wave in patients with an apical pansystolic plateau and pathological atrial wave recurs constantly throughout the material, as does a small and flat, or almost absent, rapid filling wave in the case of patients with an apical or parasternal pansystolic plateau wave and normal atrial wave.

## 6 SUMMARY OF CHAPTER VI

Chapter VI discusses in more detail the distinction between the normal late systolic plateau of the apexcardiogram and the pathological pansystolic plateau. Criteria for differentiation are defined on the basis of the shape of the plateau and its height in relationship to the total amplitude.

Dividing the material into groups, a separate group is formed of overweight patients (group II) and of a small number of patients with pathological pulsations median to the apex in an area around the parasternal line (group III). The main group of patients (group I) contains 139 cases, and a comparison of palpation findings with those on the apexcardiogram shows that the apical beat in 10 of the 36 patients with a normal late systolic plateau on palpation was found to be probably heaving. Findings in the normal material, results of the radiological examinations, and the later course show that it is the precordial palpation which gives disappointing results and not the apexcardiography.

However assessment by palpation does

not only give relatively numerous false positive findings. In the same group 22 persons were found to have a definite pansystolic plateau wave in the apexcardiogram. A definite heaving apical beat could be ascertained in four of these cases only whilst 15 were recorded as probably heaving. The radiological findings and further course showed convincingly in these cases too the reliability of the apexcardiography compared with precordial palpation.

In the normal material the apical tracing never showed an atrial wave exceeding 30 per cent of the total height of excursions in systole. Findings in the patient material suggest that a pathologically enlarged atrial wave must be considered to be a reliable indicator of an enlarged and and probably failing heart, even if it appears as an isolated finding.

In overweight persons (group II) results of apexcardiography seem to be much more uncertain though apexcardiography still shows itself considerably more reliable than palpation findings.

Group III consists of 15 cases with a localized heaving impulse median to the apex in an area around the parasternal line. Registration corresponding to the centre of this impulse showed a definite pansystolic plateau wave in 13 cases, and a probable plateau in the remaining two. The patients concerned, with one exception, had all had a large anterior or antero-septal infarction and a common feature of the group is an ECG with persistent slight to moderate ST elevation in several precordial leads, usually most marked in V<sub>3</sub>-V<sub>4</sub>.

These cases obviously have persistent abnormal midprecordial pulsations fol-

lowing a large anterior wall infarction. Myocardial aneurysm was demonstrated by radiography in only one of these cases. Eight cases were examined by electrokymography but findings were negative, or uncertain except in the case with cardiac aneurysm verified on radiological examination.

The prognostic significance of a pansystolic plateau wave in the apical tracing is considerable, with or without the presence of pathologically enlarged atrial wave.

On follow-up 23 patients died from their cardiac diseases during the period of observation, which was 14-48 months, average 28 months.

The great majority of patients who developed cardiac failure, and about half the patients who died belonged to the group showing a pansystolic plateau wave in the apical tracing.

A pathologically enlarged atrial wave occurring as an isolated finding also appears to imply a grave prognosis. This applies to an even greater extent to the cases showing a pansystolic plateau wave both in the apical tracing and the left sternal tracing, even though numbers in each of these latter groups are few.

Phonocardiographic findings supplement well those of regional cardiography. In the entire patient series, a 3rd heart sound, 4th heart sound, or both, were recorded in 28 cases. A total of 19 of

these 28 cases were found in that part of the material which developed cardiac failure and/or died. All but one of these 19 later developed cardiac failure, and 10 subsequently died.

Electrocardiographic criteria of left ventricular hypertrophy as given by Sokolow & Lyon were found, however to be unreliable when used in coronary heart disease.

Observations made in the normal series indicated already that the use of voltage in precordial leads, as a criterion of left ventricular hypertrophy gives too many false positive findings.

Similar observations were made in the patient series, as judged by results of electrocardiography compared with findings on radiological examination. Though a number of patients with cardiac hypertrophy do not necessarily have cardiac enlargement, the discrepancy between the two investigations is so considerable that an unreasonably large number of patients would be required with cardiac hypertrophy without enlargement, in order to change this conclusion. The value of criteria based on ST T deviations is reduced considerably by the fact that ischemic heart disease *per se* as well as use of digitalis, often results in changes which may be indistinguishable from those used in diagnosis of left ventricular hypertrophy.

## Ballistocardiography

### 1. GENERAL REMARKS ON METHOD EQUIPMENT AND SOME PREVIOUS INVESTIGATIONS

The small movements imparted to the body at each heart beat, which one may sometimes be aware of provide the clinical basis for the ballistocardiography. These movements are considerably more prominent in patients with aortic incompetence, and one may observe occasionally that each beat results in a caudal, followed by a cranial movement in rapid sequence.

Great interest arose when Starr in 1939 revived the work carried out by Gordon (1877) Henderson (1905) and others, in recording these impulses, and especially after he maintained that this type of investigation, called ballistocardiography had diagnostic as well as prognostic significance in certain types of heart disease (92-93).

Cardiac activity is the acting ballistic force. The impulse fired is actually the blood volume expelled at each heart beat. Each systole results in a to and fro movement of the body—a displacement which occurs at a certain velocity and acceleration.

These components of movement may be recorded individually or simultaneously by use of appropriate transducers and registering instruments. Transducers registering displacement are photoelectric

or piezoelectric, or devices designed on the strain-gauge principle. The magnet coil arrangement registers velocity. Acceleration may be registered by means of transducers which generate directly a signal proportional to acceleration, or indirectly best by means of simple differentiation of signals from a velocity transducer. Thus correct recording of impulses as they present themselves to the transducer is no difficult matter today. The changes which these impulses are subjected to prior to the transducer have, however, raised problems of a practical and theoretical nature, problems which have not been too easy to solve and which actually represent a considerable obstacle to the practical application of ballistocardiography.

The ballistocardiographic examination is carried out with the patient lying on a bed or platform constructed for this purpose, or on a heavy rigidly fixed table. Investigations have been performed mainly of the body's movement in a craniocaudal direction.

Starr *et al.* in 1939 constructed their high frequency undamped platform or bed weighing about 22 kg, which, when loaded had a natural frequency of 10-15 cycles per second, depending on size of load. The recording was performed optically.

Nickerson & Curus (1944) presented a critical evaluation of the method, and described their low frequency critically

damped platform weighing approximately 16 kg and with a natural frequency of 1.5 cycles per second. Movements were recorded by a capacitive device coupled to an amplifier and an ink writer.

Dock & Taubman (1949) described a method of recording the movements directly from the body, the subject lying down on a rigidly fixed table. Recording was made from the shin by various transducers of the displacement type or by magnet-coil arrangement. This method, mainly the magnet-coil arrangement with integrating and differentiating networks (68, 88, 100) found widespread clinical use because of its simple and practical equipment.

In normals, vibrations of cardiac origin with frequencies up to 2.5-3.5 cycles per second are demonstrated, and even higher frequencies in pathological conditions (100). The majority of cardiovascular impulses, however, are located in the frequency range 1-1.2 cycles per second (100).

We know too little about the changes these impulses undergo during transmission through the body.

Transference from body to the underlying surface occurs mainly through a layer of skin, subcutaneous tissue, fat, and muscles. The connection between the subject's body and underlying surface is therefore, relatively loose. The consequence is that the body, as a response to impulses, will be able to oscillate to and fro on this layer and at a frequency which is surprisingly constant (about five cycles per second).

These properties of the human body as a swinging mass, present three major problems in ballistocardiography:

1. Passive afterswingings.
2. Resonance effect.
3. Relative movement between bed and body.

Resonance effect and passive afterswingings are most prominent on using Dock's direct method, which of necessity works at the body's own frequency of about 5 cycles per second. Attempts to alter the properties of the body in this respect, retaining the direct method (76, 102, 104) did not result in substantial alteration of this fact. The amplitude distortion at the actual frequencies is accompanied by non-linear phase shift at the same time.

Starr's method suffers from the same drawbacks. The problem of relative movement between body and bed will arise in all methods in which the impulse is transferred to the transducer via a movable bed or platform, especially on mounting the pickup on the bed (100). The skin-bar method is complicated by difficulties in eliminating relative movement between pickup and body (89). Errors introduced by the platform are greater the heavier its weight and the stronger its connection to earth.

It is well known that one of the most important requirements in motion measurement is that the natural frequency of the measuring instrument should be far removed from the frequency of the motion being measured (89). Constructing a platform which, when loaded, is of a natural frequency high enough to be outside the ballistocardiographic frequency range, is both technically difficult and introduces new sources of error (100). These systems, when loaded, will, in addition, maintain their character of two

mass systems (89) and will cause resonance effect in the area around the natural frequency of the respective systems.

Nickerson's low frequency platform has, by virtue of its low natural frequency though still within the actual frequency range, and by its properties as a mechanical integrator (100) possibilities of recording body displacement in a correct manner. Degree of displacement of a body gives little information, however as to the acting force, but acceleration does (force = mass  $\times$  acceleration).

These experiences all point in one direction, to the ultra low frequency platform. This records true acceleration throughout the ballistocardiographic spectrum under certain conditions.

Burger *et al* (1953) used Gordon and Henderson's method of a platform suspended by four ropes and Henderson's pendulum principle (10-42) to obtain a sufficiently low natural frequency. Other workers (74-78-99-112) have described systems for body support with similar properties. The spring coupling of platform to ground is less than one fiftieth the stiffness of the body springs, and so excites them negligibly and the fundamental resonance is placed an octave or more below heart frequency (100). The only aperiodic support described is the lightweight bed of Talbot *et al* (1954) floated on mercury. The others are periodic, i.e. they naturally return to and swing around a median position after being moved out of equilibrium.

Ultra low frequency beds have the disadvantage of having a natural frequency in the region of the respiratory frequency (about 0.3 per second). So disturbances from respiration are prominent.

Rappaport (1955) stipulates that ultra low frequency platforms should not have a weight above 7 lbs., or a damping above 20 per cent of the critical and the natural frequency should be no greater than 0.3 cycles per second. It is obvious that, at minimal platform weight and damping, the platform and body will swing as a whole and a gradual increase in weight and damping will result in an increasingly incorrect picture of the forces to be measured. On the other hand, one may well use a somewhat heavier platform and still obtain correct reproduction of body movements, if contact between bed and body is increased, as is done by means of foot board and shoulder straps (78-100). Engineering difficulties, especially resonances, encountered with the ultra light platforms (77) are a reason for choosing this latter method, as one must take into consideration the increased stability and durability of a somewhat heavier construction.

Indeed, most workers in this field (10, 78-80, 112) employ somewhat heavier platforms and to some extent a greater degree of damping (10, 80) than recommended by Rappaport.

The literature contains numerous publications on appearance of the ballistocardiogram in coronary heart disease. Scarborough *et al* (1952) reviewed the more important publications with the methods available at that time and conclude (p. 30)

The practical diagnostic value of ballistocardiography in the study of patients with coronary artery disease is still somewhat uncertain. The bulk of evidence indicates that an abnormal ballistocardiogram may be expected in a high propor-

tion of patients with symptomatic coronary disease. However the high incidence of normal records in young patients with coronary disease and the high incidence of abnormal records in older clinically normal persons necessarily makes for caution in clinical interpretation. The use of stress tests in conjunction with ballistocardiography may be of considerable value, but it should be pointed out that while exercise increases the incidence of abnormal records in patients with coronary disease it also increases it in normal subjects as well.

This conclusion is still valid today 10 years later. There are no doubt many reasons why further progress has been so modest, the main one being presumably that coronary heart disease does not, of itself, give specific ballistocardiographic changes.

The ballistocardiogram as it appears in young adults has been used as the starting point and norm. Increasing deviation from this norm is observed with increasing age: reduction in amplitude, changes in form, and increased respiratory variations (7). These deviations have been considered to be signs of cardiovascular disease. Their diagnostic value, however, was always in doubt, owing to the lack of specificity and the high incidence with which they occur in apparently normal subjects in older age.

The prognostic significance of ballistocardiographic abnormalities is also open to dispute. Start & Wood (1961) use the greatest excursions in the ballistocardiogram, the vertical distance between peak of I wave and top of J wave, in their studies of the prognostic significance of ballistocardiography. They find that

amplitude decreases gradually with increasing age. The decrease is in the order of 1.4 per cent per year.

Persons in their normal material who originally showed very small amplitudes in the ballistocardiogram later died or suffered from cardiac disability chiefly coronary heart disease, in far greater numbers than those with large ballistocardiograms.

Their Tables show, as is natural, that the older persons develop heart disease. On eliminating the reduction of amplitude accompanying increasing age, the predictive value of the ballistocardiogram becomes relatively small and its diagnostic value in individual cases also very limited.

It is questionable whether more information in this respect may be obtained from ballistocardiography than, for example, the serum cholesterol level (§1b).

One hoped that the ultra low frequency method would give reliable results and a more clean-cut differentiation between healthy and diseased people in older age (73-75).

Using this method the acceleration tracing differs in appearance from, and shows more details than the tracing in earlier methods (73-77-99). Interest has been concentrated mainly on the normal appearance of the tracing, and the possible hemodynamic etiology and significance of the various details.

Scarborough *et al* (1958) analysed tracings obtained in 100 normal subjects under the age of 40 years, with reference to the amplitude of the more important waves, their timing, and individual variability in wave pattern.

Little information is available on in-



mass systems (89) and will cause resonance effect in the area around the natural frequency of the respective systems.

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with a view to secure how a natural frequency might be desired (Noordergraaf 1956 pp 97-100).

A natural frequency loaded and unloaded, of 0.13 cycles per second has been chosen as most appropriate. Damping factor 0.629 A footboard would, but shoulder straps are not employed because to be effective, they would have to be so tight that they would cause discomfort to the patients.

### The damping device

Eddy current damping is used.

The part of the damping equipment attached to the bed consists of a coil of fine copper wire on a small aluminium box, weighing 100 gm. The other part consists of a large portable electromagnet. Degree of damping is adjustable by means of the current supplied to the electromagnet, and can be varied from enough to well above the values actually required. Determination of degree of damping was carried out by the method of Burger *et al* (10). The bed is loaded with a gradually increasing weight, and the damping required to obtain 'overshoot' is the displacement tracing corresponding to 20 per cent of the critical value determined. The degree of damping is then varied, and proved to be completely adequate under the conditions for recording employed.

### The transducer

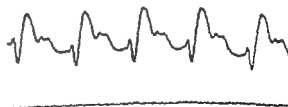
Various forms of sensing device may be used for registering bed movements. A modified version of the bar-magnet and coil arrangement (88) is used in this investigation.

The magnet is a 6 x 1 cm alnico bar magnet attached to one end to the foot of the bed. The coil consists of approximately 150,000 turns of fine copper wire being 8 cm long and having an inner diameter of 1.7 cm. The coil is placed in a small hollow cylinder together with the required differentiating and integrating network and the attenuators for calibration purposes. A test with the magnet in place in the coil field yielded uniform response in a range of at least 2.5 cm. Adjustment of the magnet return the coil field does not, therefore, present any problem. High-pass or low-pass filters are not used. Interference from alternating current and vibrations due to noise in the building may both be disturbing when using this equipment. However both difficulties could be overcome, by careful choice of amongst other things, the room for the examinations.

### Calibration (of the transducer)

A small variable speed motor is used for calibration purposes. It has a rotating

Fig. 19 Relative movement between bed and body is illustrated. Two calibrated transducers of magnet-coil type with integrating and differentiating circuits are used. Each millimetre on the paper represents displacement of 2 microns. The upper tracing shows displacement registered by the usual method, with the magnet attached to the foot end of the bed and the coil attached apart from the bed. The lower tracing shows synchronous registration of the displacement tracing, with the coil attached to the bed and the magnet to the skin of the test subject. Relative movement between bed and body is seen to be minimal. The test subject weighed 45 kg.



eccentric causing the magnet to move to and fro after being placed far enough into the coil so that the magnetic field remains constant during the calibration.

The magnet moves at constant amplitude (6 mm) and frequency (4 cycles per second) whilst the output signal of the transducer is recorded. The degree of diminution of signal output is known both as regards displacement, velocity and acceleration. All the data required to calculate sensitivity of the transducer are, therefore, available. Amplitude control of the electrocardiograph is used to obtain exactly the required amplification.

The equipment is calibrated as follows. Each millimetre displacement on the tracing corresponds to 7 microns, each millimetre velocity to 0.1 mm/sec. and each millimetre acceleration to 3 mm/sec<sup>2</sup>.

#### *b) Method of examination and grouping of material*

Identical methods were used in the examination of both normal controls and patient series. The examination was carried out at least two hours after a meal, and at least half an hour after smoking in the case of smokers.

Synchronous registration of the following tracings was carried out during suspended respiration after quiet expiration. Acceleration ballistocardiogram, apexcardiogram, phonocardiogram in the 25 cycles/second band, and electrocardiogram (the second standard limb lead).

Equipment used to record precordial pulsations was then removed, and synchronous registration of displacement, velocity and acceleration ballistocardiogram, and the same ECG lead, was then

carried out. This investigation was also performed during suspended respiration, but in the following three phases of respiration following quiet inspiration, following quiet expiration, and after deep expiration. One aimed at investigating, firstly, under which conditions the ballistocardiogram could best be reproduced. Secondly one wished to be able, if required, to assess size and shape of the different waves during both quiet expiration and inspiration.

Tracings obtained with suspended respiration following quiet expiration were found to be the most easy to reproduce whilst following deep expiration amplitudes were often variable, presumably due to Valsalva effect in some cases. Tracings following quiet inspiration were also more variable, but maintained their normal appearance longer than the others. This tracing was also often more or less disfigured by muscular disturbances. The tracings obtained after quiet expiration were, therefore, the only ones used in this study.

The displacement and velocity tracings were not used in this study. Acceleration tracings only were studied in more detail. As regards nomenclature I refer to a publication on the topic edited by Scarborough & Talbot (1956).

When a person holds his breath, amplitude of the ballistocardiographic excursions remains unchanged for a short period and then diminishes slowly. The measurements carried out here were made on the first part of the tracing, prior to commencement of decrease in amplitude of the wave complex. Measurements were made on the acceleration tracings taken after removing equipment for recording pre-

cordial pulsation, partly because this equipment weighs 1.5 kg but mainly because registration of the apex beat itself when prominent, can lead to distortion of the H wave in a synchronously recorded ballistocardiogram. The reason for this finding is unknown.

The base line was drawn using the stable mesodiastolic part of the wave. The size of the H wave and I wave was measured vertically from the base line as well as the vertical height of the IJ segment and Jh segment. h denotes the lowest point in this section of the tracing prior to its rise towards the small positive L wave (Fig. 20).

Size of N wave reckoned from the base line and the vertical distance between peaks of M and N were also measured. The latter MN distance was the only one used.

The normal and patient series were divided into age groups, as shown in Tables 7 and 8 where the number of persons in each group is also tabulated.

All overweight cases and those with hypertension — determined according to criteria previously defined for both ma-

terials — were excluded. In order to obtain as comparable materials as possible, all patients with a cardiac volume exceeding 450 ml/m<sup>2</sup> in the first instance were also excluded.

The size of excursions is given in millimetres for the sake of simplicity. Acceleration expressed in mm/sec.<sup>2</sup> is obtained by multiplying by three the number of millimetres.

### 3 RESULTS

Table 7 shows that from youth until 45–54 years of age, normally a relatively considerable decrease in amplitude of the largest excursions in the ballistocardiogram, the IJ segment, occurs. This is due to a gradual reduction of amplitude of both I and J waves. In the two oldest age groups, size of these waves remains, however practically unchanged. Size of H wave and MN segment remains nearly unchanged from the younger to the older groups, in contrast to the marked reduction of IJ amplitude mentioned above.

Further younger age groups show relatively a considerably greater difference

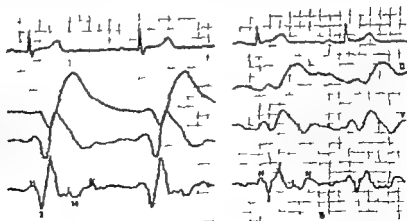


Fig. 20. Normal ballistocardiograms at (a) 20 years of age and (b) 50 years of age. Reading from above downwards: displacement, velocity and acceleration tracing.

between size of the IJ and Jh section than is the case in older age.

Despite the absence of the youngest age groups in the patient material, it is clear that precisely similar tendencies, and practically to the same degree, are present. Tables 7 and 8 show that there is

no distinct difference between the average size of the various waves in the normal and patient series, though the waves in the IJK-complex may be slightly smaller in the patient material.

The size of waves is seen to vary considerably from person to person in both

Table 7 Size of the more important waves in the acceleration ballistocardiogram in different age groups in the normal series

Amplitude in IJK portion of the tracing decreases steadily in the 45-54 year age group remaining unchanged in the two oldest groups. H wave and size of MIN show no distinct change with increasing age. Figure expresses mean and range of the various waves in millimetres. Acceleration expressed in mm/sec is obtained by multiplying by three the number of millimetres

| Age, years | < 30         | 30-44       | 45-54       | 55-64       |
|------------|--------------|-------------|-------------|-------------|
| Number     | 22           | 35          | 36          | 18          |
| H          | 3.3 (2-5)    | 3.7 (2-7)   | 3.3 (1-7)   | 3.8 (1-9)   |
| I          | 8.8 (6-16)   | 7.8 (3-17)  | 6.0 (2-12)  | 5.2 (3-7)   |
| J          | 10.1 (8-15)  | 8.5 (4-17)  | 6.7 (3-15)  | 7.3 (5-11)  |
| IJ         | 19.0 (14-30) | 16.0 (7-31) | 12.6 (6-21) | 12.5 (9-17) |
| JK         | 13.4 (10-18) | 11.5 (6-18) | 10.2 (5-17) | 10.6 (7-14) |
| MIN        | 3.8 (4-11)   | 3.2 (3-8)   | 4.6 (2-8)   | 6.0 (2-12)  |

Table 8 Size of the different waves in the acceleration tracing in normotensive patients with normal weight and cardiac volume not exceeding 450 ml/m<sup>2</sup> body surface. Figures express mean and range of the various waves in millimetres. Material divided as for normal series but with no youngest age group. IJK portion decreases in amplitude with increasing age as in normal material. H wave and MIN remain unchanged

| Age, years | < 30 | 30-44       | 45-54       | 55-64       |
|------------|------|-------------|-------------|-------------|
| Number     | 0    | 15          | 45          | 33          |
| H          |      | 3.5 (2-6)   | 3.6 (1-6)   | 3.3 (2-6)   |
| I          |      | 6.0 (2-12)  | 3.2 (2-9)   | 4.8 (2-9)   |
| J          |      | 6.7 (4-12)  | 6.2 (3-12)  | 6.6 (3-10)  |
| IJ         |      | 15.6 (8-24) | 11.4 (5-19) | 10.4 (5-17) |
| Jh         |      | 12.4 (4-16) | 9.3 (4-17)  | 9.5 (5-16)  |
| MIN        |      | 5.6 (3-8)   | 5.0 (3-9)   | 5.0 (3-9)   |

materials, but no marked difference in this respect is seen in the Tables comparing normals and patients. The figures found indicate that distribution of wave size in the two materials is fairly similar.

Graphical illustration of wave size in normal subjects and patients aged 45-54 years (Fig. 21) confirms this. Standard deviation in the same two groups is very similar as shown in Table 9. Difference of mean on no occasion exceeds twice the standard error and is not significant at the five per cent level.

Simple quantitative measurements of size of the more important waves obviously cannot differentiate between per-

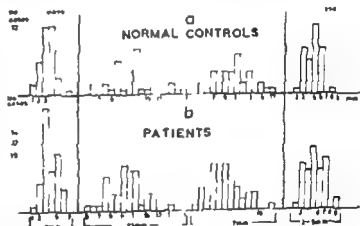
sons with or without uncomplicated coronary heart disease.

As the size of the ballistocardiographic excursions remains unchanged in the two oldest age groups, these groups are combined in Table 10. All these cases had a relative cardiac volume of 450 ml or less. This group comprises 78 persons, who are compared with persons in the same age group showing radiological borderline volumes (455-500 ml/m<sup>2</sup> body surface) or cardiac enlargement (more than 500 ml/m body surface). Further the cases who had, or later developed, cardiac failure are tabulated separately.

A tendency to further reduction of

Fig. 21 Distribution according to size of the main waves in the age group 45-54 years for a) Normal control - 34 cases. b) Patient group - 45 cases. Numbers on abscissa indicate height of waves in millimetres.

It is seen that there is only slight difference in the distribution.



amplitude of the IJ segment will be observed, but the differences are insignificant. Size of H wave and MN segment are maintained, showing rather a tendency to increase along with increase in cardiac size or in patients who had, at some stage, had cardiac failure.

It is difficult to evaluate the qualitative changes in the ballistocardiogram. The normal ballistocardiogram obtained in young people has a characteristic appearance, despite some individual variation. Figs. 20a and 22 show examples. The latter figure shows, in addition,

*Table 10 Normotensive patients with normal weight in the 45-64 year age group. Height in millimetres; the most important waves in the group with relative cardiac volume not exceeding 450 ml compared with the same waves in patients with relative volume between 455-500 ml in patients with relative volume exceeding 500 ml, and in patients in the entire group with clinical manifest cardiac failure at some point during the observation time. Increasing size of the heart or tendency to failure accompanied by a small decrease in the height of waves in the IJK part of the ballistocardiogram whereas the H wave and MN part tend to increase.*

| Roentgen volume | ≤ 450 ml/m <sup>2</sup> | 455-500 ml/m <sup>2</sup> | > 500 ml/m <sup>2</sup> | Failure group |
|-----------------|-------------------------|---------------------------|-------------------------|---------------|
| Number of cases | 78                      | 16                        | 19                      | 15            |
| H               | 3.6 (1-6)               | 4.3 (2-7)                 | 4.0 (1-6)               | 4.2 (1-7)     |
| I               | 3.0 (2-9)               | 4.9 (3-7)                 | 4.3 (1-8)               | 4.3 (1-8)     |
| J               | 6.4 (3-12)              | 5.6 (3-9)                 | 5.4 (3-9)               | 4.9 (3-9)     |
| IJ              | 10.9 (3-19)             | 10.3 (4-18)               | 9.5 (3-15)              | 9.0 (3-13)    |
| JK              | 9.5 (4-17)              | 8.5 (5-13)                | 8.8 (4-13)              | 7.7 (5-14)    |
| MN              | 5.0 (2-9)               | 5.5 (2-8)                 | 5.5 (4-12)              | 5.1 (4-7)     |

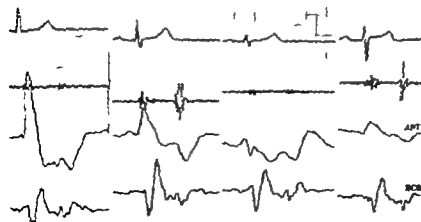


Fig. 22. Acceleration ballistocardiogram in four normal persons aged 18-39 years related to synchronous registered pericardiogram. The H wave is to some degree deformed (see text).

relationship between the acceleration ballistocardiogram and the apexcardiogram. Peak of L wave coincides with the 2nd heart sound, and the apexcardiogram too shows the relationship of this wave to the end of systole. The MN segment is related to the first part of the rapid filling period.

The marked reduction in amplitude of IJ segment in older age gives the acceleration ballistocardiogram a plump appearance (Fig. 20b). More or less marked splitting of the HIJ section often occurs at the same time and K increases in depth (Figs. 23a and 23c).

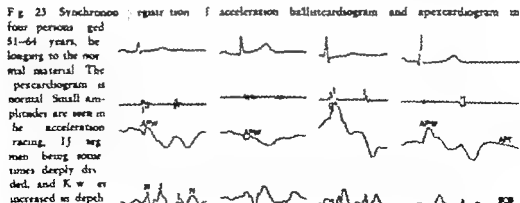
These changes occur however in so large a number of clinically healthy older persons, that it is difficult to ascribe to them diagnostic significance.

In cases with cardiac enlargement and commencing failure, very marked splitting may occur in the waves of the acceleration tracing corresponding to the first part of systole, and abnormal waves may appear. Amplitude of IJh section (Fig. 24b) may become further decreased, and H wave may become the largest

wave in the ballistocardiogram. In some cases the MN segment may increase enormously in size, with or without a concomitant protodiastolic gallop (Fig. 24c).

This type of pattern, large amplitude of H wave or MN segment or both, combined with very small amplitudes in the main part of the complex, might be a usable diagnostic pattern. Many single observations indicate that this pattern appears to no little extent in cases with cardiac enlargement or commencing failure. However the variability is considerable, and the transition to such a type of tracing is gradual making it difficult to establish definite limits. One assumes it to be doubtful whether the diagnostic or prognostic value of this type of pattern, quantitatively or qualitatively can be greater than that of the more simple demonstration of a heaving apical beat or a diastolic gallop.

The main point is that ultra low frequency ballistocardiography judging by my own and others investigations (17) appears to give as little information as





previous methods, concerning differentiation between the main bulk of patients with uncomplicated coronary heart disease and those who are clinically healthy.

The investigation presented here is based on the resting ballistocardiogram. Different stress tests do not, however, appear to improve the results to any definite extent (17).

#### 4 SUMMARY OF CHAPTER VII

Chapter VII gives an account of results of ballistocardiographic investigations using an ultra-low frequency bed and a calibrated magnet-coil velocity transducer with integrating and differentiating networks. Acceleration tracings only were used, and results given in millimetres. Acceleration expressed in  $\text{mm/sec}^2$  is obtained by multiplying number of millimetres on the tracing by three.

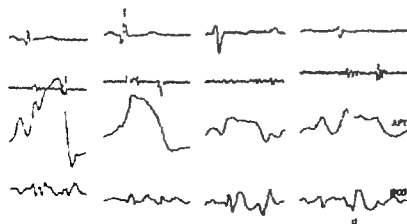
All overweight cases and those with hypertension were excluded from the patient material, using the criteria described, a total of 34 persons. From the remaining part of the patient material 130 persons, are also excluded, in the first instance, all cases with a cardiac volume exceeding  $450 \text{ ml/m}^2$  body surface.

The group of patients left, 93 cases, are considered to be as nearly as possible commensurable to the normal material. Both these materials are divided into age groups. The vertical height of the more important waves in the ballistocardiogram is measured, and findings in the two groups compared.

Findings in the normal material show that from youth to the age group 45-54 years, a relatively considerable reduction of the largest amplitude in the ballistocardiogram, the IJ segment, occurs, owing to a gradual decrease of both I and J

Fig. 24 Acceleration tracing in four patients with parasympathetic plateau tracing in their aortic diagram

- a Acceleration tracing shows very small amplitudes and marked splitting during the initial phase of systole.
- b Minimal amplitude of IJ segment. H wave is relatively tall.



- c. MN segment is the greatest wave in the tracing and is associated with protodiastolic gallop

- d. A V block grade I visible atrial sound, pathological atrial wave and synchronous with this wave a pathological (?) wave in the acceleration tracing.

waves, whilst the H wave and MN segment remain unchanged.

Precisely similar tendencies, and to approximately the same extent, are observed in the patient material. It is obvious that such simple quantitative measurements of the size of the more important waves cannot differentiate between persons with uncomplicated coronary heart disease and those without.

As the size of excursions in the ballistocardiogram remains unchanged in the two oldest age groups, 45-54 years and 55-64 years, the two groups are combined. This group then comprises 78 patients with a relative cardiac volume not exceeding 450 ml, and is compared with cases in the same age group with borderline volumes, and cases with volumes exceeding 500 ml/m<sup>2</sup> body surface as well as with those who had, or later developed, manifest cardiac failure.

Increased cardiac size or cardiac failure is associated with a tendency to further reduction of the amplitude of the IJ segment, whilst H wave and MN segment remain the same size or show a tend-

ency to increase, though the difference is negligible.

Qualitative changes in the ballistocardiogram are difficult to assess. Marked reduction of amplitude of IJ segment in older people results in a more plump appearance of the ballistocardiogram. More or less considerable splitting in the HIJ section occurs at the same time, Jh segment increasing in depth. These findings, however occur so often in clinically healthy older subjects that evaluation of possible diagnostic significance at present is difficult.

A pattern which appears in a significant number of cases with severe coronary heart disease, cardiac enlargement, and possibly commencing failure is that of a large amplitude of H wave or MN segment or both, combined with very small amplitudes in the main part of the complex. This small group however plays a minor role quantitatively. Further variability is considerable, the transition is gradual, and sharp borders are difficult to define.

## CHAPTER VIII

### General conclusions

In the present study a normal series comprising 111 men and a series of 184 male patients with coronary heart disease are examined systematically and thoroughly by usual methods, clinical, electrocardiographic, and radiological.

Using the methods described both series are then examined by means of regional cardiography (the apical tracing and left sternal tracing) phonocardiography and ballistocardiography (the low-frequency bed acceleration tracing).

The following conclusions are presented on the basis of these investigations

*Clinical methods* are uncertain as regards demonstrating cardiac hypertrophy and mild degrees of cardiac enlargement.

Palpation, as a means of assessment of the presence or absence of a heaving apical impulse, all too often gives doubtful or false results.

Demonstration of milder degrees of cardiac enlargement based on the position of the apical beat is also not easy for various reasons, even if one disregards the problem that the apical beat is all too often not palpable. The limits between normal and pathological are not very exact, depending to some extent on, amongst other factors, the intercostal space in which the apical impulse is located.

Using *regional cardiography* it has been possible, on the basis of findings in the normal material to define the limits of normal variations in both the apical tracing and in the left sternal tracing. Previous investigations by other authors leave doubt as to whether a systolic plateau wave normally occurs in the apex cardiogram. In the present work, a pansystolic plateau wave was not found to occur normally but in 24 persons in the normal material (22 per cent) the usual deep inversion of the curve during the ejection phase of systole was found to be replaced by a more or less high late-systolic plateau. Criteria for separating this from the pathological pansystolic plateau are presented.

The findings made show that a definite pansystolic plateau wave in the apex cardiogram is of considerable diagnostic significance. It provides an effective correc-

tion of the palpation findings and also gives positive information in cases where radiological examination does not allow definite conclusions to be drawn.

Confirmation was obtained of the observation of Harrison and co-workers that the size of the atrial wave in the apex cardiogram does not, under normal circumstances, exceed 30 per cent of the total excursions in systole. Furthermore it is only exceptionally of this size, i.e. in a few cases when the total excursions are small. Findings in the patient series show that a pathologically enlarged atrial wave can be regarded as a reliable indicator of an enlarged and possibly failing heart. Observations in a small number of cases indicate that this is also the case when a pathologically enlarged atrial wave appears as an isolated finding.

Right cardiac catheterization was performed in 23 patients, for purposes not connected with this work, using a technique described earlier. Results of regional cardiography and radiological examination were compared with resting pressures in the lesser circulation.

Interest was centred mainly on the relationship between the pulmonary capillary pressure and a pathological atrial wave and a pansystolic plateau in the apical tracing, or between right heart or pulmonary artery pressures and a pansystolic plateau in the left sternal tracing.

All the three methods mentioned yielded normal results in 15 cases, and in a further three cases a doubtful degree of cardiac enlargement on radiological examination was the only positive finding. Results in the remaining few cases do not allow conclusions as to a possible relationship between pressures in the lesser

circulation and the findings on regional cardiography

Follow-up studies revealed that the prognostic significance of a pansystolic plateau wave in the apical tracing is also considerable, with or without a simultaneous pathologically enlarged atrial wave. At some time during the period of observation 25 patients developed signs of manifest cardiac failure and 23 died from their cardiac disease. In the entire material 16 patients were found with a definite pansystolic plateau wave in the apexcardiogram. Twenty of these 16 patients developed signs of cardiac failure and 12 died, signs of failure being absent in only one of the deceased.

Pathologically enlarged atrial waves, occurring as an isolated finding, also appear to imply a grave prognosis. This applies to an even greater extent to the cases showing a pansystolic plateau wave both in the apical tracing and the left sternal tracing, even though numbers in each of these latter groups are few.

A localized heaving impulse median to the apex in the area around the parasternal line was found in 13 patients. Recordings corresponding to the centre of this impulse showed a definite pansystolic plateau wave in 13 of these cases, and a probable plateau in the remaining two. In all but one case the patients in question had had extensive anterior or antero-septal infarctions, and a common feature in this group was the ECG finding of persistent, slight to moderate elevation of the ST segment in several precordial leads, usually most pronounced in  $V_3$ - $V_4$ . These cases obviously have persistent abnormal mid precordial pulsations following a large anterior wall infarction. Myocardial

aneurysm was demonstrated by radiography in only one of these cases. Eight cases were examined by electrokymography but findings were negative or uncertain, except in the case with cardiac aneurysm verified on radiological examination.

*The phonocardiographic findings* provide a good supplement to regional cardiography. In the normal material a visible 3rd heart sound (rapid filling sound) was present in one person only over the age of 35 years, whilst a visible 4th heart sound (atrial sound) was found in three persons. In the entire patient material a 3rd heart sound, a 4th sound or both, were recorded in 28 cases. A total of 19 of these 28 cases were found in that part of the material which developed cardiac failure and/or died. All but one of these 19 later developed cardiac failure, and 10 subsequently died.

*Electrocardiographic criteria* of left ventricular hypertrophy as given by Sokolow & Lyon, were found however to be unreliable when used in coronary heart disease.

Observations made in the normal material indicated already that use of voltage in precordial leads as a criterion of left ventricular hypertrophy gives too many false positive findings.

Similar observations were made in the patient material as judged by results of electrocardiography compared with findings on radiological examination. Though a number of patients with cardiac hypertrophy do not necessarily have cardiac enlargement, the discrepancy between the two investigations was so considerable that an unreasonably large number of patients would be required with cardiac hypertrophy without enlargement in or

der to change this conclusion. The value of criteria based on ST-T deviations is reduced considerably by the fact that ischemic heart disease *per se* as well as the use of digitalis, very often results in changes which may be indistinguishable from those used in diagnosis of left ventricular hypertrophy.

### *The ballistocardiographic investigations*

Patients with overweight or hypertension were not included in this part of the study.

Findings in the normal material show that from youth to the age group 45-54 years, a considerable reduction of the largest amplitude in the ballistocardiogram, the IJ segment, occurs, owing to a gradual decrease of both I and J wave, whilst the H wave and MN segment remain unchanged.

Precisely similar tendencies, and to approximately the same extent, are observed to be present in the patient material. It is obvious that such simple quantitative measurements of the size of the more important waves cannot differentiate between persons with uncomplicated coronary heart disease and those without.

Increased cardiac size or cardiac failure is associated with a tendency to further reduction of the amplitude of the IJ segment, whilst H wave and MN segment remain the same size or show a tendency to increase though the difference is negligible.

Qualitative changes in the ballistocardiogram are difficult to assess. Marked reduction of amplitude of IJ segment in older people results in a more plump appearance of the ballistocardiogram. More or less splitting in the HIJ section occurs at the same time, JK segment increasing in depth. These findings, however occur so often in clinically healthy older subjects that evaluation of possible diagnostic significance at present is difficult.

A pattern which often appears in cases with severe coronary heart disease, cardiac enlargement, and possibly conduction failure, is that of a large amplitude of H wave or MN segment or both combined with very small amplitudes in the main part of the complex. This small group however plays a minor part quantitatively. Furthermore, variability is considerable transition is gradual, and sharp borders are difficult to define.

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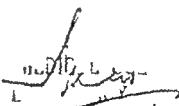
# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 405

## PHENACETIN AND RENAL DAMAGE AT A SWEDISH FACTORY

By

KURT GRIMLUND

S I. S.   
2/3/64

ACCOMPANIES VOL. 174

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HUSKVARNA 1963

Owing to the restriction of imports there was a shortage of medicines and drugs during the Second World War and the post war period. Phenacetin and medicines containing the drug were rationed, and the pharmacies at Huskvarna and in the neighbourhood soon encountered a difficult situation, for the demand for Hjortons preparation considerably exceeded the supply. Many of the P.T.s ultimately found it necessary to obtain their "powder" by mail from other pharmacies, located from Kiruna in the north to Malmö in the south.

It was prescribed by a decree of the Swedish Medical Board (1947 section 42) that when acetyl salicylic acid and phenacetin were sold loose without a prescription the package should bear the inscription "Varning. This medicine can cause injury. It should not be given to children unless prescribed by a doctor." The decree in section 43 of the same year relating to caffeine reads "Caffein, when sold without a prescription, shall be made up in packeted doses not exceeding 0.1 g each." This restriction of individual liberty was circumvented by the P.T.s by taking a powder consisting of 0.1 g of caffeine together with a Hjortons powder."

### Survey of the literature

At the 1951 symposium on N-acetyl p-aminophenol (NAPA) an important new analgesic, the chief break-down product of acetanilide and phenacetin, the only report of any adverse effect was one on 2 cases of agranulocytosis after administration of this drug for a period. The drug was considered to have largely the same antipyretic and analgesic effect as the parent substances, but did not cause methaemoglobin to form to the same extent (9). In 1953 however a report by

Spühler & Zollinger (47) of a connection between chronic interstitial nephritis and excessive consumption of phenacetin gave rise to intensive research in Switzerland, Denmark and other European countries (6 11 13 23 17 25 31). An association between renal papillary necrosis and excessive consumption of phenacetin over long periods has also been demonstrated (3 16 24).

Many researchers have doubted or even refuted any association between phenacetin and renal damage (39 40, 43 44) on the grounds of the difficulty of producing analogous renal damage in laboratory animal experiments. In 1956—58 Miescher and other workers produced renal damage in laboratory animals by long term supply of analgesics and intravenous injections of *E. coli* (26, 49 50). Reubis (40) experiment, reported 2 years later however threw doubt on the reliability of these findings, but they have since been confirmed.

The research of the last year or two has challenged the validity of Reubis' supposition that phenacetin nephritis was nothing other than primary chronic pyelonephritis, the insidious symptoms of which — headache and backache — led in turn to an increase in the amount of phenacetin taken. In an increasing number of cases it is being found that the renal damage was preceded by phenacetin consumption over a long period of years.

In more recent years there has been an increasing tendency to consider the connection between phenacetin and renal damage as established, and the research is being centred more on attempts to explore the point of attack of phenacetin.

While a number of different theories have been advanced it seems to be generally agreed that phenacetin itself cannot

Table 1 Deaths from uraemia at Huskvarna 1952-61

|                     | 1952 | 1953 | 1954 | 1955 | 1956 | 1957 | 1958 | 1959 | 1960 | 1961 | Total |          |
|---------------------|------|------|------|------|------|------|------|------|------|------|-------|----------|
|                     |      |      |      |      |      |      |      |      |      |      | No.   | Per cent |
| Total population, ♂ | 3    | 6    | 7    | 5    | 6    | 6    | 8    | 8    | 11   | 8    | 68    | 78       |
| ♀                   | 1    | 4    | 3    | 3    | 2    | 0    | 1    | 1    | 2    | 2    | 19    | 22       |
| Factory workers, ♂  | 3    | 3    | 5    | 4    | 5    | 5    | 7    | 5    | 7    | 8    | 54    | 76       |
| Confirmed P.T.s, ♂  | 2    | 1    | 1    | 2    | 3    | 3    | 5    | 5    | 7    | 6    | 35    | 51       |

cause the related renal damage. One theory is that the phenacetin produces a locus minoris resistentiae thus increasing the susceptibility of the kidney to haemotogenic and ascending infection even of mild degree (12, 41-53). An individual factor has been suspected as the reason that only some of the P.T.s contracted renal damage (45-46, 50). Hypertension (19) and allergy (14) have also been suggested as co-factors. In the latter connection attention has been centred on 4-chloroacetanilide, which occurs as a bi-product of the preparation of phenacetin from 4-nitrochlorobenzene. The fact that this method has apparently been used only during the last 20 years may explain why the injurious action of phenacetin has not come to light until quite recently.

Ask Uppmark (1) suggests the possibility of a constitutional factor on the basis of a family of which 4 members of different generations developed severe renal damage as a result of taking large quantities of phenacetin drugs for migraine. The discrepancy between Swiss and German findings in this field would seem to have been increasingly resolved in recent years for in Germany the danger associated with the rapid increase in the abuse of analgesics has been realized, the medical-social aspects of the problem have been examined and the necessity for plac-

ing phenacetin drugs on the prescription list has been considered (27).

In spite of the enormous consumption of analgesics in the United States, it was not until 1960 that a case was reported (30) in which a woman died from uraemia after abuse of phenacetin drugs. In 1961 Lakay (18) reported a case of renal damage in Canada after phenacetin abuse in which there was a distinct improvement and regression of the renal damage after phenacetin had been discontinued.

In 1962 came the first reports from Holland and South Africa of chronic interstitial nephritis resulting from excessive and prolonged consumption of phenacetin. One such case was published by Grougts in Holland (10) and 2 by Levin in South Africa (21).

#### Deaths from uraemia among abusers of phenacetin

In the last decade the number of deaths from uraemia at Huskvarna had increased to such an extent as to give rise to the suspicion of some hitherto undetected cause. Accordingly an examination of the causes of death at Huskvarna was carried out for the 10-year period 1952-61.

Table I surveys the deaths from uraemia due to chronic renal disease during this period. The figures do not include



Owing to the restriction of imports there was a shortage of medicines and drugs during the Second World War and the post war period. Phenacetin and medicines containing the drug were rationed, and the pharmacies at Huskvarna and in the neighbourhood soon encountered a difficult situation, for the demand for Hjortens preparation considerably exceeded the supply. Many of the P.T.s ultimately found it necessary to obtain their powder in small amounts from pharmacies located from 7 km to 110 km north to Malmö in the south.

It was under the leadership of the Swedish Society for the Prevention of Alcoholism (Svenska Föreningen för Alkoholprevention) that a study was made of the use of phenacetin in Sweden. The study was carried out by a committee of the Society, and the results were published in 1958. The study was made in order to determine the extent of the use of phenacetin in Sweden, and to determine the effect of the drug on the body. The study was made in order to determine the extent of the use of phenacetin in Sweden, and to determine the effect of the drug on the body. The study was made in order to determine the extent of the use of phenacetin in Sweden, and to determine the effect of the drug on the body.

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Many researchers have doubted or even refuted any association between phenacetin and renal damage (39, 40, 43, 44) on the grounds of the difficulty of producing analogous renal damage in laboratory animal experiments. In 1956-58 Miescher and other workers produced renal damage in laboratory animals by long term supply of analgesics and intravenous injections of E. coli (26, 49, 50). Reubens (40) experiment, reported 4 years later however, threw doubt on the reliability of these findings, but they have since been confirmed.

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|---------------------|------|------|------|------|------|------|------|------|------|------|-------|----------|
|                     |      |      |      |      |      |      |      |      |      |      | N     | Per cent |
| Total population, ♂ | 3    | 6    | 7    | 5    | 6    | 6    | 8    | 8    | 11   | 8    | 68    | 73       |
| ♀                   | 1    | 4    | 3    | 3    | 2    | 0    | 1    | 1    | 2    | 2    | 19    | 22       |
| Factory workers,    | 3    | 5    | 5    | 4    | 5    |      | 7    | 5    | 7    | 8    | 54    | 76       |
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Table I surveys the deaths from uraemia due to chronic renal disease during this period. The figures do not include

Table II Deaths from uraemia among P.T.s at the Huskvarna factory

| Case     | Age | Occupation    | Onset of illness | Died from uraemia |
|----------|-----|---------------|------------------|-------------------|
| 1 G. L.  | 58  | Accountant    | 1951             | 1952              |
| 2 N. J.  | 44  | Fitter        | 1950             | 1952              |
| 3 A. J.  | 63  | Turner        | 1953             | 1953              |
| 4 G. J.  | 55  | Repairer      | 1954             | 1954              |
| 5 A. A.  | 56  | Grinder       | 1955             | 1955              |
| 6 K. K.  | 52  | Founder       | 1955             | 1955              |
| 7 G. K.  | 56  | Fitter        | 1953             | 1956              |
| 8 V. K.  | 64  | Foreman       | 1956             | 1956              |
| 9 A. W.  | 63  | Driller       | 1955             | 1956              |
| 10 H. R. | 50  | Examminer     | 1956             | 1957              |
| 11 E. D. | 65  | Lift-operator | 1956             | 1957              |
| 12 A. P. | 63  | Driller       | 1955             | 1957              |
| 13 B. B. | 56  | Tinsmith      | 1953             | 1958              |
| 14 E. D. | 61  | Polisher      | 1958             | 1958              |
| 15 O. K. | 51  | Fitter        | 1957             | 1958              |
| 16 L. L. | 39  | Repairer      | 1957             | 1958              |
| 17 H. S. | 56  | Turner        | 1958             | 1958              |
| 18 E. H. | 60  | Foreman       | 1958             | 1959              |
| 19 S. H. | 53  | Filer         | 1958             | 1959              |
| 20 K. L. | 64  | Founder       | 1958             | 1959              |
| 21 R. L. | 56  | Founder       | 1955             | 1959              |
| 22 K. J. | 67  | Turner        | 1958             | 1959              |
| 23 K. N. | 59  | Blower        | 1957             | 1960              |
| 24 G. K. | 68  | Engraver      | 1957             | 1960              |
| 25 G. S. | 43  | Turner        | 1957             | 1960              |
| 26 G. S. | 43  | Welder        | 1959             | 1960              |
| 27 G. N. | 66  | Grinder       | 1959             | 1960              |
| 28 B. D. | 70  | Founder       | 1959             | 1960              |
| 29 A. I. | 43  | Tinsmith      | 1959             | 1960              |
| 30 G. A. | 56  | Fitter        | 1960             | 1961              |
| 31 H. J. | 62  | Electrician   | 1960             | 1961              |
| 32 V. A. | 70  | Carpenter     | 1960             | 1961              |
| 33 F. F. | 58  | Founder       | 1960             | 1961              |
| 34 N. B. | 69  | Repairer      | 1959             | 1961              |
| 35 W. G. | 50  | Gunsmith      | 1960             | 1961              |

Proteinuria recorded in 1922; occasional episodes since then.

Proteinuria recorded in 1918

deaths from uraemia due to acute nephritis or to urinary tract obstruction by stones, tumours, hypertrophy of the prostate and similar conditions. Cases of diabetes were also excluded. One of the most striking features is the disproportionate male mortality — 78 per cent against 22 for the women. According to the statistics for the whole country published by the Central Bureau of Statistics, the difference between the sexes in respect of death from uraemia is quite small when calculated on the same basis as the figures for the Huskvarna series. The figures for 1958, for instance, were 53 and 47 per cent for men and women, respectively.

Eighty per cent of the men were employed at the factory and 65 per cent of these were known to be regular P.T.s.

Table II surveys the deaths from uraemia among the P.T.s over the past decade. In only 2 of these cases was there earlier data on pathologic findings in the urine. The cases were evenly distributed throughout the company with no prevalence in any particular occupation. In fact it is perhaps surprising that there were not more cases from the foundry where the heaviest and dirtiest work is done, and under hot conditions.

It is perhaps notable that the period of illness was generally short, it ranging from less than one year to 3 years. For most of the cases, 26 out of 35 the period was about 12 months or less and in only 2 did it reach 4—5 years.

The amount of phenacetin taken in the individual cases can, of course, be estimated only approximately but to judge from statements by relatives, foremen and fellow workers, it was estimated at about 10 kg and in some cases considerably more.

Most of these cases have been reported by Nordenfelt & Ringertz (33) with spe

cial reference to the pathologic findings. From this study it is found that the mortality from uraemia among men at Huskvarna was six times greater than among those at Jönköping, a larger town 180 metres only away. The case histories disclosed no urinary tract infection or renal damage of any type that might account for the phenacetin abuse.

#### *Phenacetin consumption at Huskvarna and the rest of Sweden*

It has been extremely difficult to obtain a proper impression of the daily consumption of each powder-taker owing to their negative attitude to the investigation. In some sectors of the factory the resentment was manifested in overt burning of the questionnaires.

At the first interview with a powder taker at the Consulting Department one often met with a categorical denial of phenacetin consumption, and only when it was pointed out that evidence of renal damage had been found at the examination did the employee yield. It may be assumed that in general the figures relating to the powder consumption were on the low side. The older workers that had not taken the powder seemed to think that 10–15 powders a day (5–6 g phenacetin) was formerly not uncommon.

During the interviews with powder takers it was often stated by way of excuse that a similar practice prevailed at other factories throughout the country. An enquiry among physicians engaged in industries at various places in Sweden showed that this was certainly not the case. Since it was suspected that there might nevertheless be a certain excess consumption, a questionnaire was sent to the pharmacist in a number of industrial towns in different parts of Sweden requesting information on the annual sales

*Table III Estimated consumption of phenacetin at six Swedish towns*

| Town         | Population | Consumption of phenacetin 1939 |              |
|--------------|------------|--------------------------------|--------------|
|              |            | kg                             | g per capita |
| 1 Huskvarna  | 13,000     | 700.0                          | 54.0         |
| 2 Jönköping  | 45,000     | 1,064.0                        | 23.6         |
| 3 Eskilstuna | 57,000     | 483.0                          | 8.5          |
| 4 Åresta     | 10,400     | 62.2                           | 6.0          |
| 5 Fagersta   | 15,000     | 80.3                           | 5.3          |
| 6 Västerås   | 74,700     | 398.0                          | 5.3          |

of phenacetin at the respective pharmacies.

On the basis of the resulting information Table III has been compiled which gives a survey of the annual consumption of phenacetin at Huskvarna and 5 other industrial towns comparable with Huskvarna. The figures for Huskvarna and Jönköping were considerably higher than for the other towns.

The *per capita* consumption at Huskvarna was about ten times as great as for the towns 3–6 but in fact the consumption at Huskvarna was considerably higher since a number of powder takers there made their purchases at Jönköping. It would seem that the figure of 6.0 g per capita for town 4 may be taken as the mean for the country as a whole.

The annual consumption of phenacetin at Huskvarna and neighbourhood displayed only small fluctuations over the 10-year period. In the whole country however there has been a steady increase in the consumption of analgesics since the Second World War. No reliable figures seem to be available but at a very rough estimate the total is about 50,000–60,000 kg. This may be compared with Fletcher's (36) figures for the increase in the consumption of phenacetin in Switzerland

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|----------|-----|---------------|------------------|-------------------|
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| 31 H. J. | 62  | Electrician   | 1960             | 1961              |
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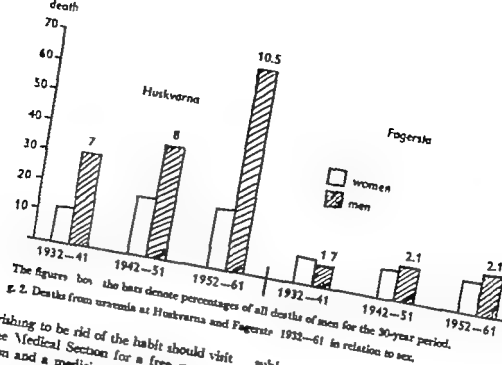
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g. 2. Deaths from uremia at Huskvarna and Fagersta 1932-61 in relation to sex.

wishing to be rid of the habit should visit the Medical Section for a free examination and a medicine that could be taken instead of the powder during the transition period. The medicine consisted of Coramine and caffeine.

At first the whole campaign was regarded in the town as a joke and many P.T.s who took advantage of the offer and attended the Medical Section were

subjected to persecution and derision by the more confirmed P.T.s. But when the number of deaths and severe illness increased among the P.T.s, the seriousness of the problem was brought home to them.

The offer of an examination and the help of the Medical Section was accepted at first by some 30 of the employees, and since spring 1939 these have been checked

Table II. *Associated reasons for taking phormic acid. Replies to questionnaire (see next page)*

| Reason for starting               |    | Reason for continuing |    |
|-----------------------------------|----|-----------------------|----|
| Pains                             |    |                       |    |
| Change of work                    | 31 | High working pace     | 28 |
| Shift work                        | 11 | Force of habit        | 16 |
| High working pace                 | 10 | Fatigue               | 10 |
| Encouragement from fellow-workers | 5  | Pains                 | 8  |
| Fatigue                           | 7  | Bad ventilation       | 3  |
| Curiosity                         | 3  | Shift work            | 2  |
| Monotonous work                   | 2  | Low wages             | 3  |
| Recommended by doctor             | 1  |                       |    |
| Discomfort                        | 1  |                       |    |
| Common cold                       | 1  |                       |    |
| Other reasons                     | 7  |                       |    |

## The questionnaire

Answer questions applicable to you and return the form whether you take "Dr HJ prep." regularly or not.

|   | Age   | Man | Woman | Department |
|---|---|-----|-------|------------|
| 1 Do you take or have you taken "Dr HJ's prep." regularly?                                | Yes   |     | N     |            |
| <i>If the answer to the first question is "yes" please answer the following questions</i> |   |     |       |            |
| 2. For how long have you been taking "Dr HJ" prep." regularly?                            |   |     | years |            |
| 3. Average consumption per day  |   |     | boxes |            |
| 4. Why did you start?   | Encouraged by older fellow-workers<br>Change to heavier work<br>Shift work<br>Owing to frequent head-aches or other pains<br>Any other reason |     |       |            |
| 5. Why do you take Dr HJ prep. now?   | Out of old habit<br>Heavy or rapid work<br>Pains or aches<br>Morning fatigue<br>Any other reason  |     |       |            |
| 6. At what time of the day do you get the best advantage of "Dr HJ" prep. ?               | Morning or beginning of the shift<br>Afternoon or end of the shift  |     |       |            |
| 7 Do you use "Dr HJ prep." also on days off and holidays?                                 | Yes   |     | No    |            |
| 8. Are you convinced of the necessity of taking the prep. to perform your work?           | Yes   |     | N     |            |
| 9 If you took the prep. earlier but now have stopped, when did you stop?                  |   |     |       |            |
| 10. Why did you stop  | Propaganda<br>Illness<br>Any other reason   |     |       |            |

regularly. Only 3 of them gave persistent pain as the reason for taking the powder 2 because of sciatica and one of migraine.

In spite of propaganda and instructional lectures the consumption of the powder appeared to continue unabated, to judge from the sales figures of the pharmacies, and it was for this reason decided to carry out a general medical examination of the employees that had been in the Company's employ for more than 5 years.

## Scope of the investigation

The investigation covered workshops which were taken as representative and involved a total of 936 persons, about one half of the factory workers.

At the time of the examination all were at work and felt in good health. All were asked whether they had earlier had any illness or disorders, especially involving the urinary tract and all were required to complete the questionnaire again, this time at a personal interview

Table V *Stated reason for taking phenacetin. Replies obtained at personal interviews with 189 employees*

| Reason for starting             | No. | Per cent | Previous reply | Reason for continuing | No. | Per cent | Previous reply |
|---------------------------------|-----|----------|----------------|-----------------------|-----|----------|----------------|
| Encouragement by fellow-workers | 105 | 56       | 7              | By force of habit     | 161 | 85       | 16             |
| Pains                           | 56  | "        | 34             | Pains                 | 14  | 7        | 8              |
| Shift work                      | 20  | 11       | 10             | High working pace     | 7   | 4        | 28             |
| Change of work                  | 14  | 7        | 11             | Fatigue               | 7   | 4        | 10             |

Table VI *Clinical and laboratory finding for 189 abusers of phenacetin*

| Total consumption of phenacetin (kg) | No. of cases | Serum creatinine >1.5 mg% |          | Dist. b. p. >100 | Hb <83% | Urinary findings |            |              |               |          |
|--------------------------------------|--------------|---------------------------|----------|------------------|---------|------------------|------------|--------------|---------------|----------|
|                                      |              | No.                       | Per cent |                  |         | Proteinuria      | Leucocytes | Erythrocytes | Hyposthenuria |          |
|                                      |              |                           |          |                  |         |                  |            |              | No.           | Per cent |
| 1-5                                  | 119          | 22                        | 19       | 12               | 26      | 6                | 4          | 4            | 18            | 15       |
| 5-10                                 | 43           | 23                        | 50       | 11               | 27      | 6                | 6          | 9            | 24            | 53       |
| 10-29                                | 25           | 19                        | 6        | 9                | 16      | 9                | 3          | 3            | 18            | 72       |
| Total                                | 187          | 64                        | 34       | 32               | 69      | 21               | 13         | 18           | 60            | 32       |

According to Bonnes & Toombs *J Biol. Chem.* 138, 581 (1945) Normal range (men) 0.8-1.3 mg per 100 ml (including serum creatinogen)

The laboratory tests consisted in a haemoglobin determination, red cell counts when the value was below 70 per cent, ESR and Heller's and Almén's tests. A urine specimen taken in the morning was subjected to a sediment examination and the specific gravity was recorded. As a renal function test the serum creatinine value was determined. For specific gravities below 1.015 a modified concentration test was performed: a fluid-free diet was given on the day the test was performed, with abstention from fluids for 20 hours. The total volume and specific gravity of the urine were recorded and the sediment was examined. Since the specimen for the concentration test had to be taken at home and no check was possible, the results could not be regarded as reliable.

However in all the cases in which the employee was sent to the Department of Medicine at Jøkkings Coaster Hospital for further examination, the specific gravity values were confirmed. The employees themselves also displayed an interest, probably realising the importance of having the test performed properly.

As a result of an examination of the 936 employees a group of 189 P.T.s was obtained. These included a number that were still taking the powder and those that had discontinued the habit after the lecture campaign early in 1959.

The reasons for starting and continuing to take phenacetin, recorded this time at personal interviews with the 189 P.T.s, are summarized in Table V. Altogether 105 or 56 per cent, stated that they had



Table IX. Clinical and laboratory findings relating to the 18 cases of renal damage among 747 professed non-PTs

| Serum creatinine (mg) | No. of cases | Diast. b. p. >100 | Hb <85% | Urinary findings |            |              |               |
|-----------------------|--------------|-------------------|---------|------------------|------------|--------------|---------------|
|                       |              |                   |         | Proteinuria      | Leucocytes | Erythrocytes | Hypo-stenuria |
| 1.5-2.0               | 13           | 5                 | 3       | 0                | 1          | 2            | 2             |
| 2.1-3.5               | 5            |                   | 4       | 1                | 3          | 2            | 4             |
| Total                 | 18           | 10                | 7       | 1                | 4          | 4            | 6             |

were considered to be PTs by their fellow-workers but they themselves firmly denied the fact.

#### *Previous urine findings*

One of the 125 PTs with normal serum creatinine levels had had proteinuria of obscure origin for many years, 11 had had haematuria on different occasions with or without episodes of renal colic. In only one case was renal calculus confirmed by urography. In one case there was chronic pyelonephritis with no symptoms. In only one case — of proteinuria — were there symptoms prior to the abuse of phenacetin.

Of the 64 PTs with a pathologic serum creatinine level 2 had previously had episodes of pyelonephritis, one had had attacks of cystitis of short duration, 11 had had haematuria, 4 of these with renal colic. Owing to the relatively mild and transient nature of the symptoms, urography or pyelography had been performed in only a few cases. The consumption of phenacetin in all 189 cases except one had started long before the first renal or urinary tract symptoms were experienced.

#### *Other clinical findings*

Of the 125 PTs with normal serum creatinine levels 13 had sought medical

advice over the last 10-year period for dyspeptic symptoms, which were diagnosed as chronic gastritis, and 14 had had treatment for gastric and duodenal ulcers, diagnosed by radiography — a total of 27 cases, or 21.6 per cent. In the same period 6 cases of chronic gastritis and 8 of gastric or duodenal ulcer were found among the 64 PTs with a pathologic serum creatinine level — 14 altogether or 21.8 per cent.

Among the 18 professed non-PTs with renal impairment (Table IX) 4 had a history of ulcer but 3 of these were strongly suspected of being PTs despite their denial, so that no reliable percentages can be obtained in this respect.

Out of the remaining 729 non-PTs 45 had gastric or duodenal ulcer and 28 gastritis — altogether 73 or 10 per cent.

#### *Prognosis for PTs after discontinuing the practice (Table I II)*

The 64 employees that displayed pathologic serum creatinine levels were followed up regularly over a period ranging from 18 months to 4 years. As a rule the follow-up examinations were performed every 3 months, but those complaining of symptoms or displaying a high creatinine level or signs of deterioration were examined every month.

Among the 41 employees with creatinine levels in the range 1.5—2.5 mg per 100 ml, there were 14 or 35 per cent, for whom the values were normalized over varying periods. In 13 the level fell distinctly while in 14 it remained unchanged or increased slowly (8 cases). One of these died from uraemia (no. 4 in the case reports). In this group there was no particular therapy or diet regime apart from discontinuation of the phenacetin consumption (with the exception, of course of the fatal case).

For the next group of 14 cases with a creatinine level between 2.6 and 3.5 mg per 100 ml the prospects seem to be considerably poorer. One half of the group had rising values and one died. In 4 the serum creatinine level remained unchanged and in only 3 cases, or 21 per cent, was an improvement recorded. Eight of the group had been treated at the Department of Medicine at Jönköping Central Hospital. The others had also been told of the renal damage and were put on a low nitrogen diet, with plenty of fluids. In some cases tonics and vitamins were given.

Seven of the 9 with serum creatinine levels exceeding 3.5 mg per 100 ml have already died from the inevitable uraemia, in spite of intensive hospital treatment. The remaining 2 have also received such treatment for advanced renal insufficiency.

### Case reports

#### *Group 1 Serum creatinine 1.5—2.5 mg per 100 ml*

**Case 1** — G. J., foundry worker aged 47 years, who had previously been in good health. In April 1959 he had consulted doctor for fatigue, and complained of headache and dizziness; on the previous day he had fainted at work. He denied taking the powder regularly. A routine examination

showed no remarkable somatic features. Laboratory tests were normal. After 14 days rest with tonics he had recovered completely.

At medical examination in August 1959 he confessed that he had been taking the powder regularly for the last 6 years in the belief that it would help him to do his work better. The estimated total consumption of phenacetin was 25 kg. He had discontinued the practice in early May that year. No somatic findings of interest. Serum creatinine 2.0 mg per 100 ml. Other laboratory tests normal. The creatinine fell rapidly to a normal level and remained steady. He had no difficulty to stop taking the powder and he worked as well as before. He no longer has headaches or attacks of dizziness.

**Case 2** — E. N., foundry worker aged 54 years, who as a rule had previously enjoyed good health and had never had any urinary tract symptoms. In 1944 he began to take the powder being encouraged by his fellow workers, so as to keep up with the high pace of work. It gradually developed into a habit that he could not give up. Estimated total consumption 10 kg. In 1949 he had been on sick leave for 2 months or so for duodenal ulcer.

December 1959. Haemoglobin 91 per cent. Heller's test negative. Sediment negative. Specific gravity 1.018. Serum creatinine 2.0 mg per 100 ml. Blood pressure 220/150. He was given sick leave for a month or two and recommended to stop taking phenacetin. After 6 months the serum creatinine was normal. The specific gravity never exceeded 1.018.

November 1962. He stated that he had been taking about a couple of powders a day (powder without phenacetin) from old habit but found them useless, of course. The blood pressure was 160/100 and except for the specific gravity the laboratory findings were normal.

**Case 3** — F. L., foundry worker aged 41 years. He could not recall any serious illness in the past. In 1951 he took sick leave for short time for lumbago, result of lifting too heavy objects. He began to take the powder in 1952, with no other reason than that all the others did so. Estimated total consumption of phenacetin about 8.5 kg.

December 1959. Except for a serum creatinine level of 1.8 mg per 100 ml all the tests were normal. He stopped taking the powder when he learned that there was damage to the kidneys. After only 6 months the serum creatinine had fallen to 0.90 mg per 100 ml. The highest value for the specific gravity since the beginning of the examination was 1.021 and the blood pressure was constantly normal.

**Case 4** — G O, a metal-plate worker aged 40 years. He could not recall any serious illness. In 1942 several of his fellow-workers were taking the powder and he too fell into the habit, so as to keep up with the others. He never pondered on why he took the powder. Estimated total consumption of phenacetin about 10 kg.

December 1959. Haemoglobin 75 per cent. Heller's test negative. Sediment negative. Specific gravity 1.016. Serum creatinine 2.1 mg per 100 ml. Blood pressure normal. He promised to stop taking the powder and by April 1960 the creatinine level had fallen to 1.1 mg per 100 ml. H was in good health and working from that time until June 1961 when he contracted tonsillitis with fever and difficulty in swallowing. Laboratory tests: ESR 69 mm. Heller's test negative. Sediment a few white cells. Hyposthenuria, specific gravity 1.011 and serum creatinine 3.75 mg per 100 ml. The infection was rapidly controlled with antibiotics and in about one month the ESR had recovered to normal.

In spite of this there was steady deterioration with decreasing haemoglobin, rising serum creatinine, malaise and vomiting. He was admitted on three occasions to the Department of Medicine in Jönköping, where he received treatment for nephropathy and uraemia. On each occasion metabolic acidosis, hypocalcaemia and hyperphosphataemia were recorded. At the last examination the serum creatinine was 29.5 mg per 100 ml and the haemoglobin 40 per cent. Death followed a few days later.

Prior to admission in February 1962 there were episodes of renal colic, with pains in the left flank. Radiographs disclosed no calculus. Neither during the examinations at the company Medical Section nor at the Department of Medicine of Jönköping Central Hospital, did any signs of urinary tract in-

fection come to light. Pathologic findings included considerable shrinkage of the kidneys and hyalinization of many of the glomeruli. There were no signs of chronic glomerular nephritis, but chronic interstitial inflammation of varying severity. Practically all the papillae visible in the sections displayed necrosis and below the tips there were cavities containing granular masses resembling calculi. There was no evidence of acute or subacute ascending pyelonephritis.

**G P** Serum creatinine 2.6–3.5 mg per 100 ml

**Case 5** — O J, a driller aged 51 years, who had previously been in good health, with no known renal complaints or infection of the urinary tract. At the age of 35 years he had begun to take phenacetin powder to keep up the pace. Estimated total consumption about 6 kg of phenacetin.

March 1960. H complained of fatigue and headaches over the last year which had obliged him to take more powder. H promised to discontinue the practice and was supplied with Coramine-caffeine tablets. Haemoglobin 72 per cent, Heller's test positive, sediment negative. Specific gravity 1.015. Serum creatinine 3.2 mg per 100 ml.

December 1960. Repeated episodes of renal colic. At the Department of Surgery no signs of mechanical obstruction were evident and the man was referred to the Department of Medicine. Haemoglobin 66 per cent, red cells 3.5 mill. Serum creatinine 3.2 mg per 100 ml. Normal calcium and phosphorus levels in the blood. No reticulocytes. Concentration tests gave a specific gravity of 1.017. No constant albuminuria. Urine cultures showed no growth. The patient was put on a diet poor in nitrogen and with abundant liquids.

There was gradual improvement with an increase in haemoglobin, decrease in serum creatinine and disappearance of the headaches. The appetite was good, there was an increase in weight and there was no longer tiredness in the evenings.

October 1962. Haemoglobin 88 per cent. Heller test negative. Sediment negative. Specific gravity 1.009. Serum creatinine 2.00 mg per 100 ml. Since May 1961 the employee had been working and there were no subjective symptoms.

**Case 6** — O H., a lorry driver aged 44 years. H was always in good health when young with no urinary tract disorders, but in more recent years he had had pains in the lumbar region. During the last ten years he had regularly taken the powder "because all the others did so". H also worked for many years as an illicit seller of powder. Headaches were frequent. Estimated consumption of phenacetin was 8.5 kg.

October 1959 Haemoglobin 67 per cent. Red cells 3.3 mill. H flier test negative. Sediment a few red cells, 15—20 white cells. Serum creatinine 3.5 mg per 100 ml. Specific gravity 1.015. Blood pressure 135/20. H took fright at the news that his kidneys were affected, probably owing to the powder and promised to give it up immediately. More over he acted thereafter as an extremely enthusiastic collaborator in the anti-powder campaign.

Except for the concentrating capacity all the laboratory values showed a steady improvement.

June 1961 Haemoglobin 83 per cent. H flier test traces of albumen. Sediment negative. Specific gravity 1.014. Serum creatinine 2.50 mg per 100 ml. Blood pressure 135/85.

On 2 occasions there was gross haematuria without appreciable urinary tract symptoms or pain. Radiographs showed no signs of calculi, but moderate ductal degeneration and deformant alterations which would explain the earlier backache.

May 1962 Acute severe pains in the right flank, dysuria and gross blood in the urine. The symptoms disappeared after a few days.

October 1962 Haemoglobin 94 per cent. H flier test negative. Sediment negative. Specific gravity 1.012. Serum creatinine 2.20 mg per 100 ml.

**Case 7** — L. L., sewing-machine worker aged 37 years. H could recall no long illnesses and had never had urinary tract infection. For decade or so he had been taking 2—3 powders a day and according to his fellow-workers and foremen sometimes considerably more. Estimated total consumption of phenacetin 7.5 kg.

September 1960 He was in good health and admitted to taking the powder formerly as he had habit. Haemoglobin 79 per cent.

H flier test negative. Sediment negative. Specific gravity 1.007. Serum creatinine 3.3 mg per 100 ml. Blood pressure 165/85. ESR 11 mm. He was put on a low nitrogen diet with plenty of fluids.

September 1961 Serum creatinine had gradually risen to 7.35 mg per 100 ml. Haemoglobin varied. From June 1961 H flier test showed traces of albumen. Sediment a few white and red cells for the first time. Specific gravity 1.012.

October 1961 admitted to the Department of Medicine. Haemoglobin 63 per cent. Blood pressure 175/100. Serum creatinine 7—8.1 mg per 100 ml.

January 1962 H flier test positive. Sediment 1— red, occasional white cells. Haemoglobin 64 per cent. Specific gravity 1.007. Serum creatinine 9.70 mg. He felt in good health, with no malaise. Put on Dianabol, Prednisone and namma. He did not wish to be admitted to the hospital for treatment.

March 1962 Appeared to be almost euphoric (he had probably continued taking powder from his stock). H flier stronger than for many years. His appetite was good, he slept well and had put on weight.

June 1962 Had been working, but was obliged to give up owing to malaise and vomiting. Serum creatinine 21.1 mg per 100 ml.

In spite of repeated blood transfusions the deterioration progressed rapidly and he died from uraemia, serum creatinine 25.0 mg per 100 ml. Both kidneys were much reduced in size and the cut surface displayed marked alterations: the parenchyma was yellowish grey with diffuse structure. Papillary necrosis with some calcification.

The macroscopic picture was one of pyelonephrosis. Several of the papillae were necrotic, some displayed calcification, others were practically ossified. There were no signs of infection.

**Group 3 Serum creatinine > 3.5 mg per 100 ml**

**Case 8** — G. N., a grinder aged 64 years. In 1932 gastric resection for duodenal ulcer was performed, since when there had been no gastric disorders. There had been no renal disorder or urinary tract infection. Since 1937 he had had attacks of uraemia.

Table X Findings relating to the 4 P.T.s that died from uraemia

| Case | Age | Abuse of phenacetin |             | Hb (per cent) |      | Serum creatinine (mg%) |      | Blood pressure (mm Hg) |         | Urinary findings |            |              |                          |
|------|-----|---------------------|-------------|---------------|------|------------------------|------|------------------------|---------|------------------|------------|--------------|--------------------------|
|      |     | Time (yr)           | Amount (kg) | First         | Last | First                  | Last | First                  | Last    | Proteinuria      | Leucocytes | Erythrocytes | Renal papillary necrosis |
| 4    | 40  | 17                  | 10          | 75            | 40   | 2.1                    | 29.5 | 140/80                 | 150/90  | (+)              | +          | (+)          | +                        |
| 7    | 37  | 10                  | 7.5         | 79            | 54   | 3.3                    | 23.0 | 165/85                 | 210/100 | (+)              | -          | (+)          | +                        |
| 8    | 64  | 20                  | 10          | 79            | 40   | 11.4                   | 19.5 | 165/90                 | 180/85  | +                | (+)        | (+)          | +                        |
| 9    | 50  | 10                  | 6           | 79            | 28   | 3.8                    | 19.5 | 165/90                 | 180/120 | +                | (+)        | (+)          | -                        |

The two columns give the first and last readings recorded.

Iron therapy was initially beneficial. Heller's test negative. Sediment negative. Blood pressure 165/90. He admitted to only a moderate consumption of the powder but his relatives and fellow-workers stated that he had been taking the powder regularly for 15-20 years and had consumed large quantities. Total consumption of phenacetin estimated at more than 10 kg.

Owing to falling haemoglobin, malaise and vomiting he was referred to the Department of Medicine. Haemoglobin 40 per cent, red blood cells 2.1 mill. ESR 83 mm. Heller's test positive. Sediment negative. Serum creatinine 11.4 mg per 100 ml. Creatinine clearance 4 ml per min. He was given fluids in quantity and 3 blood transfusions. After dismissal there was a rapid deterioration and he died in September 1960.

Microscopic examination showed an advanced picture of shrunken kidney. One papilla was distinctly necrotic and there were acute and chronic pyelonephritis in the adjacent region. The renal cortex was greatly shrunken with hyaline glomeruli and streaks of interstitial inflammatory infiltration.

**Case 9** — A. H., foundry worker aged 50 years. He had always been in good health when younger but during the previous few years he had put on weight and been suffering from shortness of breath when going up hill and limbing stairs. On occasions since 1957 he had sought advice for tiredness and dis-

ease. Blood pressure about 200/100. There was no evidence of renal insufficiency and no urinary tract infection. He admitted that he had been taking the powder regularly for the last 10 years or so but considered the amounts to be quite moderate. Nothing more than a bit of fumes. Estimated total consumption of phenacetin about 7 kg.

February 1960 Haemoglobin 79 per cent. Heller's test trace of albumin. Sediment negative. Specific gravity 1.012. Serum creatinine 3.8 mg per 100 ml. Blood pressure 165/100. He was advised to give up the powder habit immediately.

There followed a steady deterioration, with haemoglobin falling to 56 per cent. Serum creatinine 9.9 mg per 100 ml (January 1961). His relatives stated that he had not discontinued taking the powder.

After repeated blood transfusions at the Department of Medicine the haemoglobin rose from 42 to 56 per cent and the serum creatinine fell from 12.0 to 9.6 mg per 100 ml. Repeated cultures of the urine showed no infection and the sediment displayed no signs of pyelonephritis. Subsequently treatment at the Department of Medicine yielded only brief improvements. Urine cultures negative and no signs of pyelonephritis.

He died in July 1962 from uraemia. Microscopic examination disclosed marked shrinkage of the kidneys with increased interstitial connective tissue and hyalinized glomeruli. The tubules were for the most part filled with hyaline casts.

The results of the examinations on the 4 deceased P.T.s are summarized in Table V. With the exception of no. 9 the albuminuria appeared only in the very advanced stage of renal damage.

## Discussion

### *Phenacetin consumption*

Over the last few years there has been an increase in the consumption of sedatives and analgesics (7-12, 19-47). In the case of the phenacetin consumption at Hus-livarna however it reached its peak of popularity at the beginning of the 1950s, since when the sales of phenacetin drugs at the pharmacy in the town have remained fairly steady. The figure of 700 kg for the annual consumption of phenacetin is certainly a generous under-estimate. If account is taken of the amount of Hjortons powder bought in the neighbouring towns of Jönköping, 1,000 kg would be a more accurate figure. This would give a *per capita* consumption of about 77 g.

A simple calculation yields some interesting figures. If it is supposed that 1,000 inhabitants, or 7.5 per cent of the population take the powder regularly the *per capita* phenacetin consumption will then be 1 kg annually or 2.75 g a day. This is considerably above what has been regarded as the maximum safe dose (0.9-1.0 g; (28-46). It follows that on 1st February 1961 (when phenacetin drugs were placed on the prescription list) a large number of the inhabitants fell into the class of habitual powder takers and risked renal damage if they continued the practice. In spite of this, surprisingly few asked for "Hjortons powder" on prescription. Instead, the new situation was accepted and a powder was bought that did not contain phenacetin and for which no

prescription was required (0.5 g phenazone and 0.1 g caffeine). Asked what they thought of the new powder they would usually reply to the effect that it was quite useless but that one had nonetheless to take a few now and then. To judge from the sales figures at the pharmacy however the consumption of the new powder containing no phenacetin was much the same as that of Hjortons preparation prior to February 1961.

It has often been discussed whether the abuse of analgesics is a craving or merely a bad habit (34). In the present series there was not a single case of addiction, and the majority had no difficulty in discontinuing the practice. In many cases it was a pure delusion. Considerable trouble would be taken to obtain powder at a distant pharmacy reputed to make up a particularly effective one. When the pharmacist had the powder granulated there was much resentment, it being regarded as a swindle since in the new form it had "no effect at all". As a result either the powder was bought at another pharmacy or the granules were crushed by stamping on the packets.

The reason that there have been no cases of genuine addiction is probably that, unlike the Swiss preparations (28-34) this powder does not contain a sedative.

### *Effect of phenacetin abuse*

**Nervous system** — As a rule only mild nervous disturbances were found among those taking the powder regularly. A common symptom, however was finger tremor which in some cases was quite pronounced. The headache of which many complained was alleviated or disappeared entirely when the phenacetin was discontinued. The local psychiatrists have found no appreciable increase in de-

pression and mental disturbance that might be associated with the abuse of analgesics.

*Blood* — A cyanotic ashen complexion was found in about 25 per cent of the cases. After the phenacetin had been discontinued there was a rapid recovery of the normal skin hue. The typical illomened uraemic skin hue was occasionally encountered, however. Anaemia was found in only 36 per cent of the 189 P.T.s but in this respect there was a significant difference between the two phenacetin groups 1—5 and 10—29 kg, the figures being 22 against 64 per cent, respectively (Table VI).

*Kidneys* — The renal alterations found in this study would seem to be essentially similar to those that are characteristic of chronic interstitial nephritis after prolonged regular consumption of phenacetin. In no cases was there evidence of previous renal damage or urinary tract infection that might have accounted for the phenacetin habit. The date on which the phenacetin was first taken could usually be established with acceptable accuracy. It probably coincided with engagement at the factory or removal to another workshop, which was easy to check through the records at the Personnel Department.

It is highly improbable that there could have been 64 cases of pyelonephritis in which the disease progressed with no symptoms and without giving rise to pyelitis with lumbar pains and high temperature. Nor would headaches commonly regarded as being a characteristic of pyelonephritis, be got rid of by discontinuing phenacetin. This, according to Colombi (1) and others (40-43) is a criterion of chronic pyelonephritis as dis-

tinct from chronic interstitial nephritis, which often progresses without symptoms.

Negative results were obtained for most of the urine cultures, which, however were performed only in cases in which the employee was referred to Jönköping Central Hospital for examination.

There seems to be evidence that even in the absence of supervening infection phenacetin may give rise to renal damage demonstrated in this series.

If due regard is taken of the large number of P.T.s with completely normal renal status or only an impairment of the concentrating power such as is found in the early stages of chronic interstitial nephritis, it is obvious that the phenacetin cannot alone account for the renal damage. This suggests the presence of certain co-factors.

#### *Contributory causes of renal damage*

*Constitutional factors.* — In view of the results obtained by Danish workers on 4-chloroacetanilide (14) skin tests were carried out with phenacetin and 4-chloroacetanilide. Intracutaneous tests were performed with phenacetin and 4-chloroacetanilide diluted 1/10,000 in isotonic saline and patch tests were done with 1.5 per cent 4-chloroacetanilide. The tests were performed on 30 P.T.s with renal damage and on 11 of the 18 non-P.T.s with damage (Table IX). All the tests were negative, and thus provide no support for the theory that the renal damage might have an allergic origin.

Many of the families were found to have 2 or more members that took the powder regularly and had renal damage. There was a parallel with the cases reported by Ask Upmark (1) and Poli (38). Fig. 3 shows a family with 11 children, the father of whom died aged 76 from cancer of the prostate. The mother

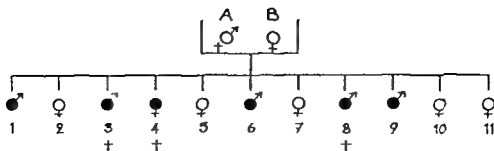


Fig. 3. Renal damage in family with 6 members (filled circles) known to have taken phenacetin regularly

is still living and is in good health for her age (78)

But of the eleven children born between 1906 and 1931 three (nos. 3, 4 and 8) have already died from uraemia aged 50, 51 and 47 years. The direct cause of death of no. 3 was supervening acute myeloid leukaemia, of no. 4 a vascular lesion. No. 8 had been admitted to Karolinska Hospital on two occasions for renal papillary necrosis and uraemia. The surviving male members of the family had all been receiving treatment since the beginning of the investigation for nephropathy with some degree of renal insufficiency. All had also been treated for gastric or duodenal ulcer and nos. 1 and 11 by surgical operation. Of the other female members no. 10 had often had treatment for anaemia of obscure cause, no. 11 had had an operation for duodenal ulcer and repeated treatment for acute episodes of pyelitis with secondary anaemia. As regards nos. 2, 5 and 7 nothing is known of any particular illnesses. All the males had admitted abuse of phenacetin. Among the female members, no. 4 denied taking powder to excess and no. 11 was strongly suspected of doing so. Nothing is known of the others.

Thus, of the 11 siblings, the 5 known to have been P.T.s and the one suspected

all displayed renal damage. Three of them had already died from uraemia. This suggests a constitutional familial factor which affects certain systems of organs, in this case the kidneys and urinary tract and also to some extent the gastric mucosa.

In addition to the above cases, there were 8 other families among the P.T.s between 2 and 4 members of which displayed mild to severe renal damage and 5 of whom had already died of uraemia.

Phenacetin nephritis is comparable to silicosis insofar as the latter runs a chronic course with only mild if any symptoms for many years, before ultimately causing 100 per cent invalidity of only some of the affected workers. In this field, too, researchers have long been discussing the possibility of a constitutional factor. In this connection interest attaches to the studies on twins by Parnisus *et al.* (34) and on the pyloric type by Beckmann (2).

**Climate** — It is perhaps surprising how few of the papers on phenacetin derive from countries with a subtropical or tropical climate. This might of course be ascribed to a smaller tendency for analgesic problems to arise there than in the more temperate countries, but in view of the narcotic problems that are encountered in the hotter countries, this ex-



planation is improbable. It would seem natural that, as a result of the increasing control of narcotics throughout the world there should be a tendency for the milder cases of narcotic abuse to change to the more readily available analgesics.

As has been pointed out earlier the various occupations were fairly uniformly distributed with respect to deaths from uraemia among the P.T.s (Table II). This was rather surprising since it has long been known that a relatively larger number of P.T.s are to be found in the foundry where the work is heavy and dirty and where the temperature is 5 to 10° above normal — that is where the employees perspire freely and tend to drink large amounts of liquid.

The foundry employed 280 men all of whom were included in the investigation; they constituted 30 per cent of the series. However only 37 such workers among the 189 employees, or 20 per cent, confessed to powder abuse. Of the 64 P.T.s with pathologic serum creatinine values (Table VII) only 5 were foundry workers (7.8 per cent). The serum creatinine level of 4 of these fell to normal only a year or so after they had stopped taking phenacetin.

The strikingly good figures recorded for the employees working in premises with an air temperature 5—10° above normal (18°C) might to some extent be ascribable to an increase in metabolism, intensive sweating and hence a more rapid fluid circulation, supply of 3—5 litres of fluids and a proportionate secretion of urine. The apparently good chance of this occupational group of resisting the fatal effect of phenacetin abuse might explain why so few cases of phenacetin damage have been reported from countries where the temperature does not differ greatly from that in a foundry.

### *Medicosocial aspects*

In recent years there has been a growing interest in social and medicosocial problems associated with the increase in the use of analgesics and sedatives (27, 28). With the rising standard of living there has been a trend towards good living at the expense of physical and spiritual vitality. The will to make an effort is lacking and instead there is a tendency to follow the path of least resistance. The national health insurance benefits have been improved to the point where in many cases one can earn as much, if not more, when on sick leave, as when working. This situation favours especially those that adhere to the principle of the maximum gain for the least effort.

It has been found, moreover, that there are cheap ways of ridding oneself of both real and imagined ailments. However in the case of prolonged consumption of phenacetin analgesics there is a risk not only of contracting renal damage but also of silencing and repressing symptoms that would otherwise oblige one to consult a doctor in time.

The 13,000 or so inhabitants of Huskvarna pay out some 200,000 kr per annum on analgesic powders not on the prescription list, in spite of the fact that one could obtain the same preparation in tablet form for about one-half the price. "The tablets have no effect."

The extreme P.T.s probably paid out some 6,000 kr for Hjortens powder over the years, and in general the cost of an annual supply must have been 300—400 kr especially as a "regular" would often be obliged to pay more for illicit supplies.

There is every reason to suppose that many of the P.T.s that gave up the powder owing to the campaign have now resumed it to the same extent on the sup-

posed grounds that, since it no longer contains phenacetin it is now harmless. One still encounters in the consulting room P.T.s that have not been registered as such, and who are on the path to uraemia. There is, however, every hope that the trend reflected in Fig. 1 will be broken now that phenacetin has been placed on the prescription list. The next decade or so will show.

#### *Aspects of occupational physiology*

Long before the beginning of the investigation the powder problem had been discussed with the employees of the Company. It was commonly held that so long as the prevailing high working pace was insisted upon by the Management, and the wages were so low, and so long as the piecework rates were incorrectly fixed so long would the employees need to take the powder to earn enough to keep themselves and their families. These views were examined closely. Since the Second World War the working tempo has gradually increased and industries today require a much greater output by their employees than formerly was the case. This is due chiefly to the greater competition on the world markets but also to some extent to the rapid technologic development, whereby better machines and more rapid techniques call for greater care and mental agility from the operators. Physical strength and effort seem to yield an increasingly poor dividend.

The person who is fortunately endowed from the physical aspect but who has an intelligence below the average is in a dangerous situation. He gradually falls into the background when appointments are made to the more responsible posts commanding higher salaries. As a result he will be advised by his fellow workers to take a few powders or tablets of one

kind or another which, he is assured, will yield undreamed-of benefits. And thus another P.T. is created.

While the problem of low wages and poor piecework rates is of course not a new one in the case of this Company it is recognized that on the whole the incomes are good. That this is so is borne out by the large number of motor cars that surround the factory on working days. The argument that the abuse of analgesics is an outcome of the high pace of work is also invalidated by an examination of the age composition: no case was found in which phenacetin was taken to compensate for the reduction in working capacity with age.

The employees among the higher age groups that had never fallen to the temptation of taking stimulants were well-adapted to their working environment, and were satisfied with the management and their comrades. They accept the lowered physical ability as inevitable and try instead to maintain their output through their experience, their ability to simplify certain operations and by as often as possible allowing the spinal cord to take over the role of the brain. They do not fall for any cheap advertisement on the excellent properties of our powder.

The P.T.s on the other hand seem to belong to a category that for various reasons readily fall to the temptation of taking powders. In this group are those that from physical or mental frailness cannot keep up with the incomes of their comrades or friend and are therefore tempted to resort to stimulants in the belief that in this way they can supplement their powers. In fact, the powder acts as a whip which forces one to draw on the power reserves of the body that normally would be available only in emergencies (8/20). Cases of repeated collapse in the

factory where careful examination revealed no pathologic changes were in all probability due to overstrain under the action of the powder.

Among the P.T.s there are those who are constantly anxious about their work. Owing to the tense situation on the labour market, even quite firmly established businesses may be obliged to scale down their activities and the threat of unemployment consequently hangs over the head of the employees. Yet others are those that are dissatisfied in their work and cannot get on with their comrades and management; these tend to resort to analgesics or sedatives, the euphoric effect of which enables them to escape from the monotony of everyday life and to see their environment in a brighter light.

### Conclusions

Phenacetin being still the analgesic in most common use every attempt should be made to ensure that it is applied in accordance with medical indications, and strict measures should be taken to eliminate the increasing abuse of analgesics as stimulants. Information campaigns would seem to be an inadequate means to this end.

*Preventive measures might well include the following*

(1) All drugs containing phenacetin or its derivatives such as NAPA should be available only on prescription (27-29)

(2) Doctors should be encouraged to recommend alternate use of phenacetin and non-phenacetin drugs in cases of disorders in which pain of long duration.

(3) Containers of phenacetin or derivative drugs should bear an inscription relating to the risk attaching to their regular use over a long period.

(4) Research on analgesics should be intensified with the object of developing effective analgesics that do not have the injurious effects of phenacetin (5-35)

### Summary

A study has been performed on the exceptionally high consumption of phenacetin at Huskvarna a Swedish town of 13 000 inhabitants with a heavy industry employing some 3 000 predominantly men. Among the employees that took phenacetin powders regularly there were 35 deaths from uraemia in the decade 1952-61 all apparently due to abuse of phenacetin drugs.

The annual consumption of phenacetin at Huskvarna was approximately 10 times as great as at Fagersta, a town of approximately the same size and character. A comparison between them with respect to the number of deaths from renal insufficiency over the last three decades showed a well-defined difference. At Huskvarna there was a steady rise in the number of deaths from uraemia, whereas in the other town the number remained more or less unchanged. During the last decade considerably more than 3 times as many males as females died from uraemia at Huskvarna.

The analgesics were taken almost exclusively for their stimulant and euphoric effect, there being only a few cases in which protracted pain was given as the cause.

The study was performed on 936 employees, representing workshops uniformly distributed throughout the factory. All had been working normally during the 12 months prior to the investigation and claimed to be in good health. Of these 189 admitted abuse of the powder and among these "healthy" persons 34 per cent

had renal damage of varying degree whereas of the 747 employees that did not take the powder only 2.4 per cent showed evidence of such injury.

There were only a few cases of super-vening infection. Unlike the series of previous studies on phenacetin, this one consisted only of males.

It is evident from the results that phenacetin cannot have been the sole cause of the renal damage. Among the subsidiary factors that may be of significance are allergy and climatic conditions. Gastric or duodenal ulcer and chronic gastritis were found in 21.6 per cent of the habitual powder takers, and in only 10 per cent of the 729 that denied the practice.

The prognosis proved poor in all cases where the serum creatinine was above 3.5 mg per 100 ml. Where the level did not exceed 2.5 there was still a good chance of an improvement provided that the phenacetin practice was discontinued. The impairment of the concentrating power will persist however.

The findings appear to confirm the view that phenacetin drugs taken over a long period may cause renal damage that in some cases has a fatal outcome. The disease runs an insidious course and symptoms are experienced only when it has reached an irreparable stage.

A routine examination with Heller's test and an examination of the urinary sediment will not as a rule reveal phenacetin damage in its initial stage, and in some cases not even when it is advanced. The specific gravity provides a more reliable indication.

The investigation seems to provide no support for the theory that some form of infection is an essential factor in this form of renal damage.

Constitutional defects possibly of a hereditary kind, are conceivable co-fac-

tors. Climatic conditions may have some influence on the occurrence of renal damage.

### Acknowledgments

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I would also like to thank Dr Olof Nordeus for his kindness in making available photostat copies of record cards from the Department of Medicine at Jönköping County Hospital. My thanks are due also to the staff of the Department who have been of invaluable help in various ways.

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# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 406

## MYOCARDIAL INFARCTION

CLINICAL FEATURES AND OUTCOME IN  
THREE THOUSAND THIRTY SIX CASES

*by*

JAN SIEVERS

*Accompanies Vol. 175*

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LUND 1964

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SUPPLEMENTUM 406

FROM THE DEPARTMENT OF MEDICINE, UNIVERSITY OF LUND, HÄLMÖ OF SÄLL HOSPITAL,  
HÄLMÖ, SWEDEN (PROFESSOR J. A. WALDEN STRÖM)

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A retrospective study of hospital records, however, places great demands on the examiner's ability to sift and evaluate data. It is attended with many sources of error and the examiner must describe the material in detail to show how much one can apply any observations made there to all cases given the same diagnosis. Many authors analyzing hospital material have failed to do this. This is one of the reasons for the partly unwarranted opinion that retrospective studies are of little value.

The present study aims to portray the various characteristics of myocardial infarction for the information of clinicians in their everyday practice. It is for this reason that I have compared the observations made in the series with data from the underlying population. I have not attempted to determine any figures for the prevalence or incidence of myocardial infarction in the population of Malmö.

The study was begun in Malmö at the beginning of the 1950's by Professor Gunnar Blörck, and Professor Blörck, Dr Gunnar Blomqvist and myself have already published a number of reports on some of the features studied in the present material (see Sievers and Blomqvist, 1962 for a complete list of references). As the investigation proceeded, it became evident that the material was suited to a more detailed presentation of the clinical characteristics of myocardial infarction than we had originally intended. Prompted by my former collaborators, therefore, I have now revised the original investigation and

complemented it with analysis of a number of special points.

Edwards (1962) wrote that "It is timely to put into practice oft-quoted phrases about the superiority of illustrations over words to employ illustrations as the dominant element in conveying ideas while a few well-chosen words simply introduce and connect the facts portrayed. I have followed his advice. That is to say I have presented all the observations I could in graphic and tabular form. Whether I have managed to link the illustrations together with words that are well-chosen, I leave to the reader to decide.

\*

The preparation of this volume was aided greatly by the interest and constructive criticism of Professor Jan Waldenström. I am also indebted to Professor Waldenström for being allowed to carry out the investigation at the Medical Department in Malmö.

The beginnings of the investigation date back to almost ten years ago, when Professor Gunnar Blörck first aroused my interest in myocardial infarction. Professor Blörck has been of great support to me throughout all these years through his enthusiasm for the work and his guidance and advice.

Dr Gunnar Blomqvist shared with me most of the time-consuming labor of collecting the material for this study and many of the data published here are the result of close collaboration with Dr Blomqvist. I am sure that few others have had the privi-

lege of working together with such a stimulating and cooperative colleague

Dr Bengt Johansson and I have had valuable discussions together on several aspects of the investigation. He and Dr Sven Nilsson kindly helped with the day to day supervision of the patients from 1961 and 1962

It is largely due to the friendly and self sacrificing assistance of the whole secretarial staff of the Cardiological Laboratory at our Department that I

am able to present the study at this date.

The Swedish National Association Against Heart and Chest Diseases defrayed a large part of the expense of collecting and treating the data.

To all these superiors, colleagues, secretarial staff and associations, I wish to express my deep gratitude.

Jan Slevers

Malmö, Sweden

November 1963



## POINTS OF ENQUIRY DIAGNOSTIC CRITERIA AND MATERIAL

Many authors writing about myocardial infarction do not define what they mean by the term. As Burch (1963) said in his summary of a large symposium on the etiology of myocardial infarction: "It was interesting that nobody wanted to define myocardial infarction but everybody talked about it, and everybody seemed to know what they were talking about."

Actually there is no sharp line of demarcation between the ischemia in the myocardial tissue resulting in the necrosis associated with infarction and the ischemia resulting in angina pectoris even the death of only a few cells, such as may accompany angina pectoris, could be called infarction. For the clinician, however myocardial infarction has come to mean a condition in which it is possible to demonstrate the necrosis in the myocardial tissue by electrocardiographic or laboratory means, and this is the way I use the term.

It is generally agreed that in prosperous societies myocardial infarction is usually the result of atherosclerotic changes in the coronary vessels, whether it is precipitated by thrombosis or by other forms of partial or total obstruction of these vessels. Our minds

are so preoccupied with this cause that we are apt to forget that other causes exist.

Autopsy was performed on 811 out of 858 patients with first infarcts who died shortly after their infarction. Five of the 811 infarcts were found to be caused by an embolus in the coronary vessels. This corresponds with the rate found in other series though the literature contains only a few reports on infarction caused by embolism (Shrader et al., 1956). If it is true that infarction of embolic origin is more often lethal than other types of infarction, this origin was probably even more rare among the survivors than 5 out of 811 would indicate.

Another possible cause is syphilis. Only 35 of all the patients in this series had syphilis and only 3 of these were reported to have had syphilitic aortitis. It was impossible to calculate how often the infarction was secondary to syphilis in this series. It is evident, however, that this origin was rare. Still other diseases including arteritis have been reported to cause occasional cases of myocardial infarction, but cases of this origin probably comprise only an infinitesimal proportion of the vast number of in-

farcts occurring in western countries in the 20th century. This is why myocardial infarction was considered to be of atherosclerotic origin in the following pages.

### POINTS OF ENQUIRY

The main points of enquiry in this study were

1 What are the characteristics of patients with myocardial infarction?

2 What are the characteristics of the onset and acute stage of myocardial infarction?

3 What is the short term and long term outlook for patients with myocardial infarction?

To answer these questions, Dr Blomqvist and I collected a series of cases of recent myocardial infarction from the records of the Medical Department of the Malmö General Hospital from 1935 through 1950. First we went through the list of patients admitted to the Department during these years, and made a separate list of all the patients with the diagnosis of myocardial infarction, cardiosclerosis and angina pectoris, with or without a question mark appended, or with any synonyms of these three diagnoses. Then we went carefully through the records of these cases, and assembled all the ones which met at least two of the following kinds of criteria

### DIAGNOSTIC CRITERIA

#### *Symptoms*

The typical chest pain of myocardial infarction was the symptom used for a criterion. If the patients had had

angina pectoris more severe pain than they had had before pain that did not respond to nitroglycerin pain of another nature pain that radiated in a different pattern pain lasting longer than usual pain coming on during rest if before it had only been precipitated by physical exertion, cold, emotional strain or eating. I also considered nausea vomiting and dizziness, or more cold sweat and mental distress than usual during attacks of angina to be symptoms of infarction.

#### *Electrocardiographic Criteria*

I used the usual electrocardiographic criteria for the diagnosis of myocardial infarction, as described by Plotz (1957) for example in his monograph on myocardial infarction.

When there was left bundle branch block, I refrained from using electrocardiographic criteria. Plotz (1957) pointed out how difficult it was to decide for or against infarction when there was left bundle branch block he referred to Somerville and Wood (1949) who were unable to establish the presence of infarction by means of the ECG in 52 per cent of their cases of left bundle branch block. After most of the present material had been analyzed, a report by Chapman and Pearce (1957 b) indicated that electrocardiographic diagnosis was possible in these cases. If it was certain that left bundle branch block was not present shortly before the infarct, and it was seen after admission, I took it to be a criterion of infarction if the symptoms and laboratory data supported the diagnosis.

### Laboratory Criteria

For laboratory evidence of infarction I studied the notations on the white blood count, blood sugar, temperature and sedimentation rate.

The ways in which the white blood count, blood sugar and temperature react in myocardial infarction are now well known. A review of the literature on the subject is contained in Forssman's (1954) extensive monograph on myocardial infarction and adrenal function, based on cases of myocardial infarction admitted to the Medical Department of our hospital from 1950 through 1953 (thus included in the present series).

The value of the sedimentation reaction for the diagnosis when there is a suspicion of infarction was first pointed out by Rabinowitz et al. (1931). They noticed that it increased on infarction, and later authors made the same observation. Plotz (1952) reported that it rose in 97 out of his 100 cases of infarction in which the diagnosis was established electrocardiographically. He said that the rate began to rise within 48 to 72 hours and usually returned to normal within 38 days.

I did not use enzymic data for the diagnosis in these cases. We have measured the serum glutamic oxaloacetic acid transaminase (SGOT) in many cases at the Department during the last five years of the period under investigation and made other forms of enzymic studies in a number of cases. I wanted to use the same criteria for the whole 1935-1959 series, however, so as to try to eliminate the

effect of a change in diagnostic method on the number of cases from year to year. For this reason I did not use any enzymic data for the diagnosis.

### MATERIAL

#### Included Cases

Altogether 2,904 cases from 1935 through 1959 met at least two of the three kinds of criteria for myocardial infarction, and in each case the history indicated that the infarction had occurred three weeks or less before the patients were admitted. These 2,904 cases were used for the basic series.

Table 1 *The 2,904 Myocardial Infarcts from 1935 Through 1959 by Order of Occurrence in Separate Case*

| Order of Occurrences                                     | Number |
|--|--------|
| First  | 2,477  |
| Second   | 332    |
| Third  | 59     |
| Fourth   | 3      |
| Recurrence of uncertain order or first infarct elsewhere | 103    |
| Total  | 2,904  |

The order of the infarcts in these cases is shown in table 1. The 103 cases in the fifth group in the table are the ones in which it was not sure how many infarcts the patient had had before, or in which the patients had been treated for their first infarct at home or at another hospital.

I divided this basic series of 2,904 into two subseries: one from 1935 through 1954 and the other from 1955 through 1959.

The 1935-1954 cases were 1,837 in

number. For these 1,837 I collected all the data for age, sex, marital status and occupation previous disease anginal pain and symptoms of cardiac decompensation before the infarction signs and symptoms accompanying and following the infarction clinical, laboratory and electrocardiographic observations during the hospital stay certain details about treatment observations at autopsy if the patient was examined postmortem.

The 1933-1939 series included 1 069 infarcts. For these cases I only noted the age and sex, the severity of the infarct, whether or not the patient died, and whether cardiac rupture was noted at autopsy if such was done. Though I recorded less details about these cases than for the others, I used the same diagnostic criteria for them, too.

The records at the Department can be relied upon throughout the whole period for information on sex age marital status and length of hospital stay. They also give reliable and almost complete data concerning treatment, and the results of simpler forms of examination, such as temperature and pulse rate. They all go into great detail on the patient's cardiac history and the signs and symptoms and course of the infarction, but I had to be careful about interpreting the information they gave on these points. The amount of laboratory data they gave varied from period to period. Most of the time however a satisfactory check was kept on the white blood count, blood sugar and sedimentation rate which were the only

other laboratory data I used for the diagnosis. I was naturally careful not to include the cases in which these tests were not done with the ones which gave normal reactions to the tests. Different numbers of electrocardiograms had been taken in the separate cases. Different numbers of leads had also been used, and so I could not make a systematic analysis of the electrocardiographic changes in myocardial infarction. I evaluated all the electrocardiograms myself independently of how others had judged the separate case, and so the electrocardiographic diagnoses are not influenced by differences from year to year in opinion on different electrocardiographic features.

Accordingly I made all my analyses of the present series with my eyes wide open for the unreliability of old records and, whenever there was any doubt about a finding, I did not include it in the analysis of the feature in question.

Only 3.4 per cent of the hospital cases of infarction in the city of Malmö during this period were not treated in the Medical Department. Most of these cases came to the Epidemic Department which always has a number of internal medicine cases in addition to patients with epidemic disease; the rest were treated at other departments of the hospital. Patients who got a myocardial infarct in another department and who were transferred to the Medical Department are included in the 2 904 cases. The basic series thus consists of 98.6 per cent of all the hospitalized cases during the pe-

## CHARACTERISTICS OF PATIENTS WITH INFARCTS

## SEX AND AGE DISTRIBUTION

As seen from table 1 2 477 of the 2 904 infarcts were the first the patient had had, judging from the recorded data. Table 3 shows these 2,477 patients divided by sex and age intervals of ten years. Figure 1 gives the same information in graphic form. This figure also shows the corresponding values found in a series from Oslo (Acta med. scandinav suppl. 315 1956) the bars denote the present material and the dots enclosed in circles the height of the corresponding values in the Norwegian series

There were 1,591 men and 886 women in this present series of first infarcts or a ratio of 1.8 men to 1 woman. This is a smaller male preponderance than that observed in several American series (Master et al., 1939 Rosen

baum and Levine, 1941 Mintz and Katz, 1947 Wright et al., 1954) It is also smaller than in several European series, including that of Gillmann (1955) It is more like that observed in other Scandinavian series it is about the same as observed by some authors (Wallgren, 1950 Lindén, 1952) while others, including Brahme and Ahlberg (1947) Helander (1949) and Eckerström (1951) observed a still smaller preponderance of males The Oslo series shown in figure 1 yielded a ratio of 1.3 men to 1 woman.

There is not much point in comparing the ratio in different series, however for it probably varies a great deal with the kinds of population from which the series are taken.

Table 4 shows the men over women quotient in the different age groups The quotient fell with a rise in age up to the age of 69 the men outnumbered the women, but less and less with each decade and from 70 on, the sex ratio was 1 to 1

In figure 2 the ratio of men to women for each of the 25 years covered by the study is plotted in a curve. The ratio ranged between 1.5 and 2.3

Table 3 *The 2 477 Cases of First Infarcts from 1935 Through 1959 by Age and Sex*

| Age       | Men   | Women | Total |
|-----------|-------|-------|-------|
| 20—29     | 1     | —     | 1     |
| 30—39     | 23    | 5     | 28    |
| 40—49     | 163   | 33    | 196   |
| 50—59     | 456   | 134   | 590   |
| 60—69     | 544   | 318   | 862   |
| 70—79     | 324   | 330   | 654   |
| 80—89     | 65    | 63    | 128   |
| 90 and on | 5     | 3     | 8     |
| Total     | 1,591 | 886   | 2,477 |

Fig 1. Age and sex distribution of patients with first infarcts. Bars = present series from 1935 through 1959. Dots = Oslo series from 1925 through 1949

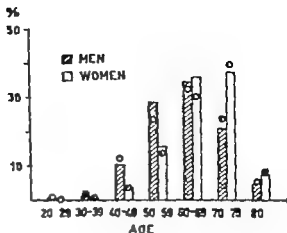


Table 4 Ratio of Men to Women in 2,477 Cases of First Infarct from 1935 Through 1959 by Age at Infarction

| Age   | Men over Women Quotient |
|-------|-------------------------|
| 20-39 | 0.6                     |
| 40-49 | 5.0                     |
| 50-59 | 3.4                     |
| 60-69 | 1.7                     |
| 70-79 | 1.0                     |
| 80-89 | 1.0                     |
| Total | 1.8                     |

to 1 the only exception was 1935 in which there was a much greater preponderance of men, but this was probably due to a coincidence as there were only 19 cases that year.

Other authors often report the mean ages of their patients. The mean age of the present 2,477 patients was 64.0 years: 62.0 for the men and 67.5 for the women. These are slightly higher means than most others have reported (Master et al., 1939; Mintz and Katz, 1947; Helander 1949; Wallgren, 1950; Russek et al., 1951; Wright et al., 1954).

Thus the present women were an

average of 5.5 years older than the men when they got their first clinically recognized myocardial infarct. Others have noted the same sex difference (Master et al., 1939; Rosenbaum and Levine, 1941; Brahmé and Ahlberg 1947; Mintz and Katz, 1947; Helander 1949; Wallgren, 1950; Lindén, 1952; Wright et al. 1954; Ekwall, 1955).

As seen in figure 3, the average age at which the men and women got their infarcts rose steadily during the

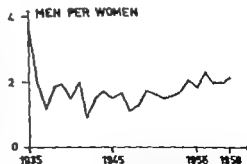


Fig 2. Ratio of men to women during different years in the 2,477 cases of first infarcts from 1935 through 1959.

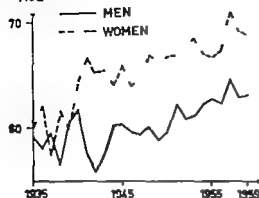
AVERAGE  
AGE

Fig. 3 Average age of men and women getting first infarct during different years 2 477 cases from 1935 through 1959

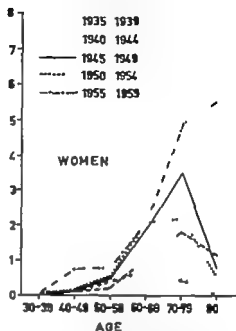
MYOCARDIAL INFARCTS  
PER 1000 WOMEN

Fig. 5. Frequency of first infarcts per 1,000 same-aged, same-sexed inhabitants of Malmö during the five year periods from 1935 through 1959. Women.

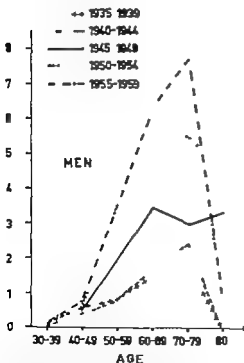
MYOCARDIAL INFARCTS  
PER 1000 MEN

Fig. 4. Frequency of first infarcts per 1,000 same-aged, same-sexed inhabitants of Malmö during the five year periods from 1935 through 1959. Men.

course of the 25 years. To see whether this rise was caused by a change in the underlying population during the course of these years, I calculated how many men and women of each decade there were to every 1 000 same-aged, same-sexed inhabitants of Malmö during each of the five year periods. Figures 4 and 5 show the results. As seen there, the infarction rate was highest between the ages of 70 and 79 for each five year period the only exceptions were the men between 1945 and 1949 and the women in the first and last five year periods. The curves thus indicate that the rise in

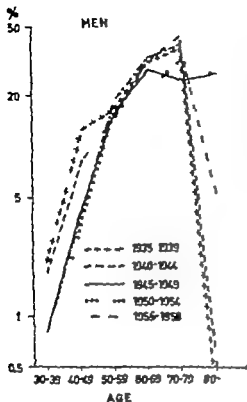


Fig. 6 Same curves as in figure 4 with difference in number of cases in different five year periods eliminated. See text.

the mean ages during the course of the years was not only caused by a change in the age composition of the underlying population. The curves in figures 11 and 7 constructed to eliminate the differences in number of cases in different five year periods, confirm this in these figures the total number of infarcts per 1 000 in the population in the five year period in question is taken as 100 per cent the curves are plotted from the percent ages of the total 100 per cent figure for which the successive age groups

were responsible. The figures show that the age of the hospitalized patients rose during the course of the years, particularly for the women towards the end of the period the proportion of old patients increased and the proportion of young ones decreased. Thus it is evident that the increase in the mean age of the patients during the course of the years was not only due to a change in the age composition of the underlying population, i.e. the inhabitants of the city of Malmö.

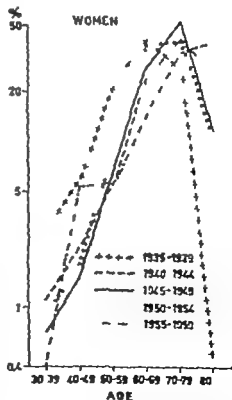


Fig. 7 Same curves as in figure 5 with difference in number of cases in different five year periods eliminated. See text.



The figures also show that during each five year period the infarcts were most apt to occur between the ages of 70 and 79. Though the average age for both sexes was between the ages of 60 and 69 these were not the ages at

which infarction was most apt to occur the mean ages are lower than the age of greatest risk, because the number of persons in the underlying population grows smaller with advancing age.

## OCCUPATION

The present series is unable to throw much light on the relationship between myocardial infarction and occupation, as the occupational statistics available in Sweden are not compiled for research of this nature. The Swedish census divides people into three occupational classes: private enterprisers, white-collar employees and working class. Private enterprisers include all people who run their own business, even if they do not employ anyone else, while white-collar employees include top executives in large concerns. Each of these classes, therefore, covers a wide range of income and responsibility. I shall give the results of grouping my series this way however as certain differences did emerge.

For the occupational analysis, I only used the cases of first infarcts from 1935 through 1954 among men who were still working when they fell ill. The women did not lend themselves to this analysis only a few were gainfully employed, and then often only part time those who kept house did very different amounts and kinds of work and they could not be grouped according to their husband's occupa-

tion, as this was often not stated in the records.

For purposes of comparison I had access to two sets of official statistics. Firstly there are figures for the percentage distribution into the three occupational groups in Malmö. Secondly there are figures for the age distribution during 1945 of the men in each of the three occupational groups in the combined cities of 30 000 and up there was little reason to assume that the age distribution in the occupational groups was much different in Malmö than for this combined population. From these statistics I figured out that the following percentages of men between 30 and 49, 50 and 64 and 65 and on were employed in each of the three occupational classes in Malmö in 1945:

|                        | 30-49<br>Years | 50-64<br>Years | Over 64 |
|------------------------|----------------|----------------|---------|
| Private enterprisers   | 56             | 27             | 17      |
| White-collar employees | 46             | 24             | 30      |
| Working class          | 43             | 15             | 42      |

Altogether 654 of the men in the 1935-1954 series of first infarcts were still actively engaged in work when they fell ill. 73 men between

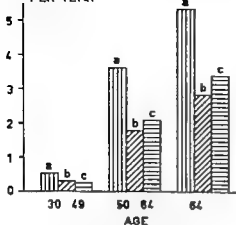
INFARCTS PER 1000  
PER YEAR

Fig 8. Number of first infarct per year during 1933 through 1934 per 1,000 male inhabitants of Malmö still fully engaged in w. k. = private enterprisers b = white-collar employees c = workers.

1935 and 1939 105 between 1940 and 1944 212 between 1945 and 1949 and 264 between 1950 and 1954. Of these, 26.4 per cent were private enterprisers, 30.1 white-collar employees and 44.5 per cent workers.

Figure 8 shows the rate of myocardial infarcts per thousand members of the three occupational classes in Malmö per year divided into three age groups. The rate was greatest among the private enterprisers, particularly from the age of 50 on there was a highly significant preponderance of men with this occupation among these cases of first infarcts. There was no conclusive difference between the white-collar employees and workers.

Figure 9 shows that the percentage of deaths within four weeks after the first clinical signs of the infarction was the same in the three occupational

classes, indicating that occupation had little to do with the frequency of hospitalization. This bears out the assumption in chapter II that the social or financial status, or both, does not affect the frequency of hospitalization in Malmö. Otherwise this might have caused the difference in figure 8.

Studies on the relationship between myocardial infarction and occupation in Scandinavia are reported in supplement 316 of *Acta medica Scandinavica* for example, and by Westlund and Hougen (1961) and Gorbатов (1961). The conditions in Great Britain have been reported by Morris et al. (1953) and Norris (1959) and American studies include those by Dawber et al. (1957) and Chapman et al. (1957a). After a review of the literature on

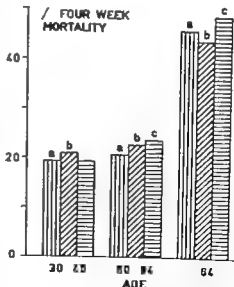


Fig 9. Four week mortality after myocardial infarction in men of different occupations. a = private enterprisers b = white-collar employees c = workers.

this subject Plotz (1957) concluded that the only thing that may safely be concluded is that coronary disease seems to occur somewhat less often among manual workers. The same applies to myocardial infarction, judging by the present figures but

there was little difference between the white-collar employees and manual laborers, and so the frequency does not seem to be solely dependent on whether or not the subjects do physically demanding work.

## MARITAL STATUS

Figure 10 shows the rate of myocardial infarction among persons of different marital status in the present series, grouped by age and sex. The married men were more liable to infarction than men of other marital status, no matter what age, and the married women of 70 and more. The difference was statistically significant for the men of 50 on and probably significant for the eldest women. Lew (1957) found the opposite, but his series covered coronary heart disease on the whole and is not directly comparable with mine. Gorbатов (1961) found an unexpectedly high rate among married women.

It is hard to explain the observations about marital status in my series. If it depended on marital status how likely the patients were to be hospitalized, there would hardly have been such large preponderances of married people, as married people have generally more opportunity of being tended at home than others. There was no difference in the four week mortality among patients of different marital status which is further evidence that it did not depend on

marital status how likely the patients were to be hospitalized.

If coronary heart disease and diet are correlated, the higher infarction

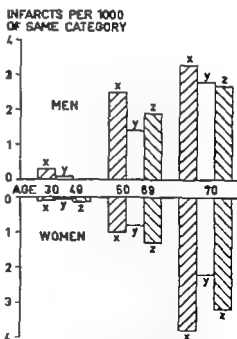


Fig. 10. Number of first infarcts per year during 1935 through 1934 per 1,000 same-aged, same-sexed inhabitants of Malmö: x = married, y = single, z = divorced and widowed.

rate among the married people might have been due to their eating more or better than unmarried people. Stress is also considered to be associated with

coronary heart disease but it is perhaps a little rash to state that married people are subjected to more stress than unmarried people

## ANTECEDENT ANGINA PECTORIS

Different authors have found different proportions of cases with preceding angina pectoris in their series of myocardial infarcts. Mintz and Katz (1947) found a rate of 72.9 per cent, and Döring and Loddenkemper (1902) about the same rate. Master and Jaffe (1952) reported 89 per cent, and others, including Ekwall (1953) and Honey and Truelove (1937) observed rates around 40 per cent. Some including Doseher and Polindexter (1950) and Westlund and Høugen (1961) give figures like 30 per cent. Doseher and Polindexter (1950) assembling 3,315 cases from 15 series in the literature, found an average frequency of 44 per cent.

Several have attempted to determine whether a history of angina pectoris affects the short term outcome of myocardial infarction. Billings et al. (1949) and Gorbatow (1961) found that it made no difference. Wright et al. (1954) concluded from their series that those who have previously experienced anginal attacks have at least as good a chance of surviving the attack as do those who have not shown this syndrome.

Because of this lack of agreement in the literature, I examined my series for the following: 1) How often was there a history of angina pectoris

before the infarction? 2) Did patients of different ages differ in this respect? 3) Did a history of angina pectoris have any bearing on the four week mortality?

There were sufficient data for analysis of these problems in 91.6 per cent or 1411 of the cases of clinically first infarcts from 1935 through 1954. For the definition of angina pectoris I followed the principles of the New York Heart Association (1953).

Table 5 *Frequency of Antecedent Angina Pectoris and Other Chest Symptoms in 1411 Cases of First Infarcts from 1935 Through 1954*

| Antecedent angina pectoris for              | No. of Cases | %     |
|---|--------------|-------|
| More than 2 years                           | 366          | 21.7  |
| 2 months to 2 years                         | 195          | 13.8  |
| Less than 2 months                          | 199          | 14.1  |
| Unstated length of time                     | 17           | 1.2   |
| Total cases with antecedent angina pectoris | 717          | 50.8  |
| Diffuse thoracic symptom                    | 254          | 18.0  |
| No chest symptoms                           | 440          | 31.2  |
| Total                                       | 1411         | 100.0 |

As seen from table 5, 50.8 per cent, or more than half the patients, had a clear-cut history of angina pectoris in all but 17 of these cases it was known how long they had had this symptom.

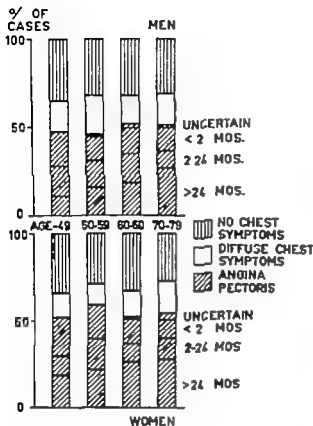


Fig 11 Percent distribution of first infarcts from 1935 through 1954 among men and women of different ages with different histories for angina pectoris.

It is hard to classify the 254 patients with a history of diffuse chest symptoms such as a feeling of pressure on the chest, or pricking and smarting sensations in the same region. Probably many of these patients did have angina pectoris but were unable to describe their symptoms distinctly. Other patients may have been led by the pain of infarction, and perhaps leading questions as well, to place undue emphasis on sensations they had had before. On the other hand both Plotz (1957) and Levine (1958) say that angina pectoris is sometimes manifested in diffuse, vague, atypical sensations in the chest. Probably

many of these 254 patients did have symptoms of cardiac origin.

In 440 cases, or 31.2 per cent of the series, the patients had no unpleasant sensations in their chest before their infarct. I.e. it was stated expressly in the record that the patient had not had any antecedent symptoms.

In figure 11 the men and women of different ages are divided according to antecedent heart symptoms. No age or sex group differed distinctly from the others in frequency of antecedent angina or vague symptoms in the chest. Thus, antecedent angina was not more common among old patients than young. On the other hand, when

Table 6. *Relationship Between Four Week Mortality Rate and Antecedent Angina Pectoris 1411 Patients with First Infarcts During 1935 to 1954 Inclusive by Antecedent Symptoms and Age at Infarction*

| Age                         | Angina More Than 2 Yrs. | Per Cent Angina 2 Yrs. to 2 Mos. | Per Cent Four Week Mortality Angina Less Than 2 Mos. | Mortality Diffuse Symptoms | % Angina |
|-----------------------------|-------------------------|----------------------------------|--|----------------------------|----------|
| 30-39                       | 10.5                    | 20.8                             | 10.0   | 23.9                       | 17.3     |
| 40-49                       | 22.3                    | 31.3                             | 17.3   | 28.2                       | 26.5     |
| 50-59                       | 37.3                    | 50.7                             | 26.5   | 33.3                       | 33.1     |
| 60 and on                   | 49.6                    | 53.3                             | 61.7   | 41.9                       | 50.9     |
| Age adjusted mortality rate | 31.6                    | 41.9                             | 32.8   | 33.8                       | 33.0     |

there was antecedent angina, it was of longer standing in the old patients with advancing age the patients with angina for more than two years increased, and the cases with a shorter history decreased. (The group in which it was not certain when the angina first started is so small that it cannot have distorted the results to any great extent.) Even on such rough comparison as between patients over and under 60 one finds a statistically significantly greater frequency of angina of more than two years standing in the older patients.

Thus it appears that old patients with myocardial infarction are not more likely to have antecedent angina pectoris than are young persons, but when they do, they tend to have had it for a longer time.

Is it because coronary heart disease progresses more rapidly in young people that, if they have antecedent angina, they are apt to have had this symptom for a shorter time than do old people. Several observations in the series indicate that coronary disease runs a more rapid, more ma-

lignant course in young people (see chap. 10).

Table 6 shows the four week mortality in the different age groups of the 1411 cases, divided according to the history of angina pectoris. It also shows the age adjusted death rates. As there was no difference between the sexes, they were combined. The only group which seems to differ from the others are the patients with an anginal history of 2 months to 2 years they seem to have a higher four week mortality rate than the others but the difference is not quite significant ( $0.10 > p > 0.05$ ) so it may have been due to a coincidence.

Judging from the foregoing, accordingly antecedent angina pectoris makes no difference to the short term outlook after infarction. Theoretically there are reasons why it should make the outlook better and why it should make it worse. The repeated attacks of ischemia in the myocardium associated with angina pectoris should lead to better development of the collateral circulation and improve the chances of surviving an infarct.

On the other hand a myocardium that is weakened by several episodes of ischemia should be in worse condition to withstand infarction than one that is not. The chances are that the ischemia works in both ways, and the favorable and adverse effect of antecedent angina cancel each other

out. It would seem so from the present series at any rate the observations there do not support the opinion of Rosenbaum and Levine (1941) that patients with antecedent angina are more apt to survive infarction than ones without.

## OTHER DISEASES BEFORE THE INFARCTION

Apart from diabetes mellitus, the hospital records for this series were not suitable for an analysis of the diseases commonly thought to be associated with infarction. It was not always possible to tell, when no other disease was mentioned in the records, whether the patients had no other disease or whether they did, but nothing was said of it in the records. Only a few of the records are so generous in detail that they state specifically that there was no evidence of this or that disease that might have had a bearing on the case.

### DIABETES MELLITUS

It has been realized for a long time that persons with diabetes mellitus are particularly prone to myocardial infarction. Schettler (1961) gave an extensive survey of the literature, and Joslin et al. (1959) also discussed this subject.

To determine what my series had to say about this relationship, I studied 1) the frequency of diabetes in the cases of first infarction, 2) the type

of diabetes occurring among these patients, and 3) the four week mortality for the diabetic patients.

Altogether 141 of the patients hospitalized for a first clinical attack of infarction between 1935 and 1954 were given the diagnosis of diabetes mellitus. In 21 of the 141 the diagnosis was made during the hospitalization for the infarction. In 11 of these 21 the patients had so vague signs of diabetes that it would probably never have been suspected unless they had been hospitalized. The diagnosis is highly debatable in these cases and the physician summing up the case in the hospital record of these patients questioned the accuracy of the diagnosis in every instance. The ones who survived the infarct never needed treatment or diet, or showed any glucosuria on re-examination. These 11 cases are therefore excluded. The other 10 cases in which the diagnosis was made on hospitalization were all clear cases of diabetes and were included in the series. This left 130 of the original 141. Table 7 shows the age and sex in these cases.

Table 7 The 130 Diabetic Patients in the 1,511 Cases of a First Infarct from 1935 Through 1954 by Sex and Age at Infarction

| Age       | Men | Women | Total |
|-----------|-----|-------|-------|
| 30-39     | 1   | —     | 1     |
| 40-49     | 1   | 1     | 2     |
| 50-59     | 17  | 6     | 23    |
| 60-69     | 23  | 27    | 50    |
| 70-79     | 15  | 35    | 50    |
| 80 and on | 3   | 2     | 4     |
| Total     | 50  | 71    | 130   |

### Frequency

One hundred and thirty cases of diabetes among the 1,511 cases of a first infarct from 1935 through 1954 is equal to frequency of 8.4 per cent 5.9 per cent for the men and 12.3 per cent for the women. This agrees with the rate Wahlberg (1963) reported or 8.8 per cent. It is lower than the rates given by American authors. Wright et al (1954) for example, found diabetes in 11.1 per cent (men 7.1 and women 24.2 per cent). Doscher and Poindexter (1950) found a rate of 11.1 per cent in a series of 2,389 cases collected from the literature (men 8.3 and women 30.0 per cent). The rates in other Swedish series have differed. Eleven out of Ekval's (1955) 232 patients with an infarct, or 4.7 per cent were diabetic, as against 13 out of Eckerström's (1931) 212 or 17.8 per cent.

In the present series there were 0.8 men to every woman with diabetes. Thus many more of the women were diabetic, as there were 1.8 men to every woman in all the cases of a first infarct. Bradley and Bryfogle (1956) and Thomas et al. (1956) ob-

served the same preponderance of women.

Despite the unreliability of old hospital records, the cases of diabetes in the present series are probably representative of all diabetic persons with a myocardial infarct, for the superimposition of myocardial infarction on diabetes is undoubtedly considered to be an urgent reason for hospitalization. A comparison between the diabetes in this series and in general should therefore yield results of interest.

### % WITH DIABETES

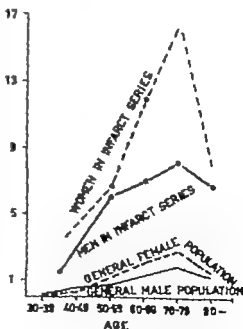


Fig 12. Percentage distribution of diabetes mellitus among men and women of different ages getting first infarct during 1935 through 1954 and among persons of the same ages and sex in the general population according to Silver and Oscarsson, 1954.



Table 8 *Ratio Between Observed and Expected Frequency of Diabetes Mellitus in 1,541 Cases of a First Infarct from 1935 Through 1934 by Sex and Age at Infarction*

| Age      | Observed over Expected Frequency |        |
|----------|----------------------------------|--------|
|          | Men                              | Women  |
| 30—49    | 8.0                              | (16.0) |
| 50—59    | 8.6                              | 5.6    |
| 60—69    | 5.4                              | 5.4    |
| 70—79    | 4.3                              | 5.9    |
| 80 and n | (5.2)                            | (5.1)  |

The figures in bracket are based on less than 30 cases.

Silwer and Oscarsson (1958) made a penetrating analysis of the frequency of diabetes mellitus in the urban and rural population of the Kristianstad county which lies in the same province of Sweden as Malmö. There is little reason why the figures for Malmö should not be approximately the same as those for Kristianstad. In figure 12 Silwer and Oscarsson's figures for the percentage of clinically evident diabetes at different ages in the urban population are compared with the same frequencies in the present series. The 30 and 40 year olds in the infarct series were pooled, as there were only 25 men and 4 women under 40. The curves for the infarct series and general population take the same course, all four reaching a peak in the 0—79 age group. On the other hand, this figure shows clearly that there was relatively more diabetes among the people with infarcts, regardless of age and sex. The same is seen from table 8 which gives the ratio between the number of observed

and the number of expected cases in different age groups

### *Type of Diabetes*

The question arises whether diabetic persons with infarcts are apt to have a particular form of diabetes. Table 9 attempts to answer this question, more particularly whether diabetic persons who get infarcts differ from diabetic persons in general in the age at which they get their diabetes. Here again I used Silwer and Oscarsson's (1958) figures for diabetic persons in general, but this time I used their combined urban and rural figures. As seen from this table, the 130 diabetic patients in this series did not differ from diabetic persons in general in ages for onset of diabetes. The quotient obtained by dividing the observed with the expected number of cases lies near 1 everywhere. In other words, when the patients got their infarcts they had had diabetes for about the same length of time on the average as diabetic people of the same age in the general population.

To see whether they differed in the amount of insulin they needed, I compared the percentage of diabetic patients who required insulin before their infarct with the percentages in the same age and sex groups in Silwer and Oscarsson's (1958) series. As seen in table 10 fewer of them required insulin before their infarct than one would expect. The difference was statistically highly significant for each age and sex group analyzed.

To sum up there was no difference between the diabetic patients and dia



**Table 10** *Observed and Expected Percentage of Cases Requiring Insulin Among the 130 Cases of Diabetes from 1935 Through 1954 by Sex and Age at Infarction*

| Age and Sex | Observed Percentage | Expected Percentage |
|-------------|---------------------|---------------------|
| Men         |                     |                     |
| 50—59       | 41                  | 73                  |
| 60—69       | 26                  | 66                  |
| 70—79       | 33                  | 61                  |
| Women       |                     |                     |
| 60—69       | 41                  | 66                  |
| 70—79       | 34                  | 62                  |

betic persons in general in age for the onset of diabetes, indicating that myocardial infarction is not more apt to occur in people with juvenile than with senile diabetes. This being so it is hard to understand why the patients with infarcts did not require insulin as much as the average person with diabetes. It may be that the physicians in Malmö had a different attitude to insulin than the physicians in the county of Kristianstad.

#### *Four Week Mortality in Diabetic Patients*

Table 11 compares the distribution into infarct classes (see chap 3) and

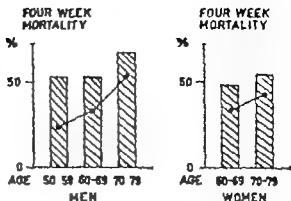
four week mortality in the various classes in the 130 cases of diabetes and in the total series from which they came,—the 1,541 first infarcts from 1935 through 1954. As seen there, the percentage distribution into different classes of infarct was the same in both. On the other hand there were many more deaths within the first four weeks in each infarct class of the diabetic series than there were in the total series the overall four week mortality amounted to 54.6 per cent in the diabetic series as opposed to 34.6 per cent in the total series. Figure 13 shows that this difference was not caused by a difference in age each age group of both sexes showed a distinctly higher mortality in the diabetic series than in the total series.

The terminal cause of death was not clear from the hospital records in 12 of the 71 deaths within four weeks in the diabetic patients. Twenty-eight died suddenly probably due to cardiac arrest or ventricular fibrillation, 16 died during an attack of pulmonary edema, and another 11 seem to have died from progressive shock. Three

**Table 11** *Diabetic Patients from 1935 Through 1959 Compared with All 1,541 Cases / First Infarcts These Years for Distribution into Infarct Classes and Four Week Mortality Rate in Each Class*

| Class of Infarct           | Patients with Diabetes |                       | Total Series |                       |
|----------------------------|------------------------|-----------------------|--------------|-----------------------|
|                            | Per Cent               | Four Week Mortality % | Per Cent     | Four Week Mortality % |
| Severe                     | 17.7                   | 91.3                  | 15.5         | 83.6                  |
| Moderately severe          | 51.6                   | 44.8                  | 62.1         | 23.7                  |
| Mild                       | 3.1                    | —                     | 3.4          | 1.2                   |
| Normal or typical ECG      | 11.5                   | 78.3                  | 7.4          | 41.0                  |
| Not detected until autopsy | 3.8                    | 100.0                 | 1.8          | 88.0                  |
| Unclassifiable             | 12.3                   | 25.0                  | 9.8          | 23.6                  |
| Total                      | 100.0                  | 54.6                  | 100.0        | 34.6                  |

Fig. 13 Four week mortality after infarction in patients of different age and sex. Curves=1,511 patients with first infarct from 1933 through 1934; bars=136 of these with diabetes.



patients died from complications, 2 from cerebrovascular lesion and 1 from pneumonia. The remaining 2 patients died while in diabetic coma.

#### HYPERTENSION

There has been much debate about the relationship between high blood pressure and myocardial infarction, as also about the relationship between high blood pressure and coronary heart disease on the whole. It seems to be the current opinion today however that the two conditions are closely related. Dawber et al. (1957) found a close correlation in their Framingham series. Chapman et al. (1957a) noted a stronger correlation in old than in young persons. There is a wide spread, however in the figures given for how often hypertension precedes myocardial infarction, rates between 30 and 70 per cent being reported (Billings et al., 1949; Eckerström 1951; Räsänen, 1951; Wright et al., 1954). It is hard to compare the figures of different authors, however for they do not all agree on

what constitutes an abnormally high blood pressure.

There were not enough data in the records of the present series for me to be able to subdivide the hypertensive cases. I had to be content with dividing the patients into ones with and without hypertension. I considered the following patients to have suffered from hypertension:

1) Patients with a systolic blood pressure over 150 or a diastolic pressure over 100, or both, on several occasions during previous hospitalization or on outpatient examinations.

2) Patients with blood pressure remaining at or about these levels during hospitalization for the infarct, even if the blood pressure before the infarct was unknown.

3) Patients who said that a physician had told them they were hypertensive, even if it could not be learned what their blood pressure was.

These about correspond with the limits Dawber et al. (1957) used for their Framingham series (high if the systolic pressure was consistently 160 or over or the diastolic pressure 100

Table 12. *Frequency of Hypertension in 1,541 Cases of First Infarcts from 1935 Through 1954 by Sex and Age at Infarction*

| Age       | Men                                   |                    | Women                                 |                    | Both Sexes                            |                    |
|-----------|---------------------------------------|--------------------|---------------------------------------|--------------------|---------------------------------------|--------------------|
|           | Whole Group /<br>No. Hyper-<br>tensiv | % Hyper-<br>tensiv | Whole Group /<br>No. Hyper-<br>tensiv | % Hyper-<br>tensiv | Whole Group /<br>No. Hyper-<br>tensiv | % Hyper-<br>tensiv |
| Up to 49  | 136/28                                | 20.6               | 31/6                                  | 19.4               | 167/34                                | 20.4               |
| 50-59     | 282/70                                | 24.8               | 88/46                                 | 52.3               | 370/116                               | 31.4               |
| 60-69     | 337/183                               | 40.7               | 226/126                               | 55.8               | 563/209                               | 46.8               |
| 70 and on | 213/66                                | 31.0               | 288/133                               | 55.5               | 431/198                               | 45.9               |
| Total     | 968/297                               | 31.0               | 583/310                               | 53.2               | 1,541/507                             | 39.4               |

or over normal when the systolic pressure was consistently below 140 and the diastolic pressure consistently below 90 and borderline in the rest of the cases)

The first two of my groups are sure cases of hypertension. The blood pressure drops after myocardial infarction (Wright et al., 1954 and Ball et al., 1955) and if it is high during hospitalization after an infarct it was probably high before as well. The cases in the third group are not so sure, though it only contained patients who had been under observation for hypertension for some time or who had received antihypertensive treatment, or both. No case was included in which the record only contained a vague reference to a visit to a physician during which the subject of high blood pressure had come up. Nevertheless, this third group may have contained some cases in which there was no antecedent hypertension. Whenever the records said too little about the pressure for exact classification, I put the case in the normotensive group.

Table 12 shows the frequency of hypertension in the cases from 1935 through 1954 divided by age and sex.

The total frequency amounted to 39.4 per cent. Up to the age of 49 it was equally common in both sexes other wise it was more common in the women.

Westlund and Hougen (1961) found hypertension in 54 out of 486 men between 30 and 64 with infarcts, or in 11.1 per cent this is a lower figure than I found. In the older Oslo series (Acta med. scandinav suppl. 315 1956) 22.2 per cent of the men and 37.9 per cent of the women had antecedent hypertension when the cases showing a diastolic pressure of 100 or more during hospitalization are added, the percentages rise to 43.8 and 62.3. Döring and Løddenkemper (1962) found similar conditions to those in table 12 a rise in frequency up to the age of 70 and then a drop. In Gorbatows (1961) series, 29 per cent of the men and 72 per cent of the women, or altogether 38 per cent, were hypertensive when the limit was put at a systolic pressure of 160 mm Hg he found no difference between his infarct series and a control series in frequency of hypertension.

There are no figures for the frequency of hypertension in the general population of Malmö. Boe et al.

Table 13. Frequency of Hypertension in Different Age Groups in the City of Bergen Norway Calculated from Figure of Boe Hamfelt and Wederwang 1956

| Age       | Percentage of Population with Systolic Blood Pressure of 155 and up |       |
|-----------|---|-------|
|           | Men   | Women |
| 20—29     | 10.25   | 3.78  |
| 40—49     | 16.97   | 18.82 |
| 50—59     | 31.51   | 41.08 |
| 60—69     | 31.46   | 66.31 |
| 70 and on | 63.63   | 8.71  |

(1956) however published an extensive study of the blood pressure in the population of Bergen in Norway. Bergen is about the same size as Malmö, and both are Scandinavian cities. Table 13 shows the frequency of a systolic blood pressure of 155 and up in Bergen at different ages. The frequency was somewhat lower than in the Malmö series up to the age of 49 but from then on it was higher in the Bergen series. It may well be that antecedent high blood pressure is not always noted in hospital records, especially in old patients, and so no conclusions can be drawn about the frequency of hypertension after 50. On the other hand, there is reason to conclude that young persons with infarcts are more often hypertensive than other persons of their age. Though the excess frequency of hypertension among them was not great, it does not tally with the conclusion of Moll and Hamacher (1962) after a study of patients under 40 with infarcts that der Hypertonus ist in der Ätiologie des jugendlichen Herzinfarktes von untergeordneter Bedeutung.

There is a difference in opinion on

whether hypertension has an effect on the short term outcome of infarction. Billings et al (1949) and others have stated that antecedent hypertension does not affect the outcome. Efring and Løddenkemper (1962) and others say it does, and signs that it does can also be seen in the series published by Eckerström (1951) and Wright et al. (1954).

Table 14 shows the four week mortality in the 1935—1954 cases, divided into those with and without hypertension. The two sets of cases show no distinct difference in four week mortality. The 14 per cent difference between the hypertensive and normotensive women of 60 to 69 is only probably significant and, judging by the rest of the figures in this table it was caused by a coincidence. Thus this table supports the opinion that hypertension does not affect the short term outlook. (The effect of hypertension on the long term outcome is discussed in chapter 7.)

#### GASTRIC AND DUODENAL ULCER

Watkinson (1956) and others have reported that ulcer is unusually common in patients with coronary heart disease. Others say it is not e.g. Wajah et al (1941), Billings et al. (1949) and Plotz (1957). There are only a few reports on the frequency of ulcer among patients with myocardial infarction. Feldman and Morrison (1951) found it in 10.5 per cent.

The cases from 1935 to 1954 in the present series contained 71 of roentgenologically verified ulcer. It was

Table 14. *Comparison Between Four Week Mortality Rate in Hypertensive and Normotensive Patients in the 1,541 Cases of First Infarcts from 1935 Through 1959 by Sex and Age at Infarction*

| Age       | Per Cent Four Week Mortality Men |                      | Mortality Women   |                      |
|-----------|----------------------------------|----------------------|-------------------|----------------------|
|           | With Hypertension                | Without Hypertension | With Hypertension | Without Hypertension |
| Up to 49  | (18)                             | 16                   | (17)              | (4)                  |
| 50-59     | 17                               | 25                   | 20                | 21                   |
| 60-69     | 35                               | 30                   | 28                | 42                   |
| 70 and on | 59                               | 32                   | 42                | 48                   |

The figures in brackets are based on less than 30 cases.

present in 11 per cent of the men under 60 and 6 per cent of the men 60 and over and in 3 and 1 per cent of the women of corresponding ages. These are lower rates than Andrén (personal communication) found in an unpublished study of the frequency of roentgenologically verified ulcer in Malmö. It may be that it was because the hospital records were incomplete in this respect that the frequency was so low among the patients with myocardial infarct. It should be possible to conclude, however that ulcer is not much more common among persons with infarcts than in the general population.

### GOUT

Ask Upmark and Adner (1950) and others have pointed out the connection between attacks of gout and myocardial infarction, and Schettler (1961) said that coronary heart disease and gout were correlated. Gertler et al. (1951) found larger quantities of uric acid in the serum of patients with coronary heart disease than in controls, and Moore and Weiss (1963) said in a recent review that the association of hyperuricemia and coronary artery

disease is as common as that between hypercholesterolemia and coronary artery disease. There are not many reports on the relationship between gout and myocardial infarction. Wright et al. (1954) found gout in 0.4 per cent of their series, and concluded that our material suggests that any occurrence of the two conditions together is purely coincidental.

There were 11 cases of gout in the present series of first infarcts from 1935 through 1954, all in men, making a frequency among them of 1.2 per cent, a higher rate than that of Wright et al. (1954). The men were 64.5 years old on the average (range 51-75 years) thus they did not differ in age from the whole series. In 2 cases, the records stated that the infarction had apparently been preceded by an attack of gout.

Whether 1.2 per cent is higher or lower than the average rate in Malmö is impossible to say for there are no studies of the frequency of gout in the population of Malmö. It would be misleading to compare the frequency with that in other parts of the world, as it varies greatly from one place to another (Hollander 1960).

## CHARACTERISTICS OF ONSET AND ACUTE STAGE OF INFARCTS

### AMOUNT OF STRAIN PATIENTS WERE UNDERGOING AT ONSET

Several authors have studied the degree of physical activity patients were engaged in at the onset of their infarcts. Later et al. (1948) said that young patients were more apt to get their attacks when they were exerting themselves than when they were resting or sleeping. Billings et al. (1940) got the impression that infarction was most apt to occur while the patients were resting and sleeping. Master and Jaffe (1952) studying 1,347 cases, found that 22.6 per cent of the patients got the attack while they were asleep, 29.8 per cent while they were resting, 22.4 per cent while they were engaged in normal physical activity, 8.7 per cent while they were engaged in more strenuous physical activity than usual, and only 1.0 per cent while they were engaged in extremely strenuous physical activity. Gertler and White (1954) found that 22 out of 90 young adults with myocardial infarction got the attack while they were resting, 21 while walking, 18 during manual labor, 11 while asleep, 8 while performing professional duties and 6 while exercising. Later et al. (1951) observed that the younger the patients were the more likely they were to

have got their attack while they were engaged in strenuous physical activity. For a comprehensive review of uncommon precipitating factors the reader is referred to Winkler (1957).

In 928 of the 1,541 cases of a first infarct from 1935 through 1954 or 60 per cent, there was sufficient information in the hospital records for an analysis of the degree of strain the patients were undergoing at the onset of their attack. I grouped these 928 patients according to whether they were resting, sleeping, engaged in or ordinary physical activity engaged in strenuous physical activity or under emotional strain at the time of their attack. By ordinary physical activity I mean the kind of work the patient did ordinarily as well as walking on level ground, less tiring forms of sport, and the like. By strenuous physical activity I mean strenuous forms of sport or heavier forms of work than the patient was used to. I classified the patients as being under emotional strain only when there was a specific statement in the record that the patients were emotionally upset when the attack came on. Unless the data in the records were quite clear I made



Table 15 *Particulars of Physical or Emotional State at Onset of Infarct in 924 Cases of First Infarct from 1935 Through 1954 by Age at Infarction*

| Age                      | Percentage |          | Cases in Age Group         |                         | Under Emotional Stress |
|--------------------------|------------|----------|----------------------------|-------------------------|------------------------|
|                          | Resting    | Sleeping | Ordinary Physical Activity | Strenuous Physical Work |                        |
| Up to 49<br>(111 cases)  | 14.4       | 22.5     | 55.9                       | 3.6                     | 3.6                    |
| 50-59<br>(349 cases)     | 17.7       | 20.9     | 47.4                       | 10.6                    | 3.2                    |
| 60-69<br>(331 cases)     | 17.2       | 26.0     | 46.6                       | 7.0                     | 3.0                    |
| 70 and on<br>(233 cases) | 25.3       | 23.2     | 45.5                       | 3.0                     | 2.0                    |
| Total<br>(924 cases)     | 19.0       | 23.5     | 47.7                       | 6.6                     | 2.7                    |

no attempt to classify the case in this respect.

One of the 928 seemed to have been the direct result of injury the patient was travelling in a bus which had to make a sudden stop and he was thrown forward, hitting his chest with great force on a hand rail he felt an intense pain in his chest and went to a physician at once definite clinical signs of infarction developed. In an other case the patient got an attack when a swarm of bees stung him on his face and head. Two patients got their infarct while they were taking a Finnish bath.

Table 15 shows the 924 remaining cases grouped according to the amount

of strain they were undergoing at the onset of the infarct. The sexes are pooled in this table, as the men and women did not differ in this respect.

As seen there, the rate of infarction during sleep or emotional strain did not differ with the age of the patients. On the other hand, the rate of infarction during rest rose with age while the rate during ordinary physical activity fell. This is probably only because old people are not as apt to be engaged in physical activity as are young people. This hypothesis is supported by the observation that age had no bearing on the frequency of infarction during sleep

## PAIN AT ONSET

It seems to be the consensus of opinion that when the pain of myocardial infarction radiates, it is most commonly referred to the left arm. Sometimes it does not radiate at all how often it

does not, is a subject of controversy (Smith et al., 1942 Chambers, 1946 Billings et al., 1949 Gertler and White, 1954 Sigler 1954 Gillmann, 1955 Kreines, 1957)

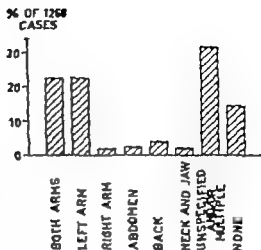


Fig 14. Percentage distribution of 1,268 patients with painful first infarcts from 1935 through 1954 according to way in which pain radiated.

In 1,357 or 88.1 per cent of the cases from 1935 through 1954 the records stated whether or not the infarction caused pain and if so, the regions to which the pain radiated. In 1,268 of these, or 93.4 per cent, the infarction was associated with pain. In the remaining 6.6 per cent it was not.

Figure 14 shows the 1,268 painful cases distributed by character of radiation. In 390 cases, or 30.8 per cent, the pain radiated in several regions, or

the records said that it radiated but not to where. This heterogeneous group is so large that one must be careful about drawing conclusions from the present series about the frequency of radiation in different directions. It will be noted, however that the same percentage of patients referred the pain to both arms as to only their left arm. This does not agree entirely with the current opinion that the pain of infarction is most apt to radiate to the left arm.

Table 16 *The 1,268 First Infarcts from 1935 Through 1954 Accompanied by Pain Grouped by Region to Which Pain Radiated and the Four Week Mortality Rate in Each Group*

| Radiated to                       | No. of Patients | % of All Patients<br>1th Pain | Per Cent Four<br>Week Mortality |
|-----------------------------------|-----------------|-------------------------------|---------------------------------|
| Both arms                         | 281             | 22.1                          | 29.9                            |
| Left arm                          | 269             | 21.2                          | 31.1                            |
| Right arm                         | 24              | 1.9                           | 20.8                            |
| Abdomen                           | 30              | 2.4                           | 28.7                            |
| Back                              | 51              | 4.0                           | 33.3                            |
| J w and neck                      | 26              | 2.0                           | 11.5                            |
| Unspecified and/or multiple areas | 390             | 30.8                          | 25.4                            |
| ^ radiation                       | 177             | 14.0                          | 29.9                            |
| Total                             | 1,268           | 100.0                         | 31.4                            |

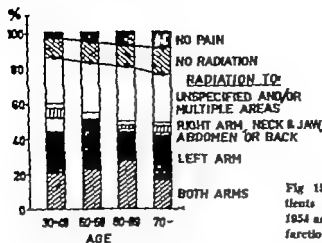


Fig 13. Percentage distribution of 1,357 patients with first infarcts from 1935 through 1954 according to their history for pain on infarction.

Table 16 shows the four week mortality in the 1,268 cases, grouped by character of radiation. The mortality was highest in the group in which the pain radiated to unspecified or many areas, and lowest in the group in which it spread to the jaw and neck. No statistically significant differences emerged, however. It may be that the patients in whom the pain radiated to unspecified or multiple areas were in worse condition when they were admitted to the hospital than the others, and the physician making the entries in the record could not be so specific as otherwise about the situation and radiation of the pain. The present series, therefore, seems to show no correlation between the character of radiation and the four week mortality.

Figure 13 shows how the character of the pain varied with the age of the patient. There is a probably significant tendency to a rise in the rate of painless infarcts with a rise in age. The cases in which the pain did not ra-

diate also rose with age, but the difference was not significant. The men and women did not differ in the kind of pain they experienced.

It is hard to judge how many patients get no pain on infarction from the present series, for it is pain that usually brings the patient to the hospital. It is not right to draw any conclusions about the frequency of painless infarction from any hospital series. One can see this from the rates given for silent infarction. Thus Snow et al. (1956) found that they ranged between 1 and 61 per cent in 25 series. Roseman (1954) observed the same discrepancy. Plotz (1957) found rates between 1 and 75 per cent in 17 series. The best way to determine the frequency is probably by making prospective studies of populations like that of Kannel et al. (1961). Stokes and Dawber (1959) found in the Framingham study that 15 out of 73 cases of myocardial infarction, or 21 per cent, had not been recognized clinically though there was unmistak-

able electrocardiographic evidence of an infarct having taken place 8 of the 15 patients said that they had not had any precordial pain Lindberg et al. (1960) found from a prospective study of more than 700 men that 3 out of 20 myocardial infarcts, or 15 per cent, passed unrecognized.

The present series contains far fewer painless infarcts (6.0 per cent) than the series of Lindberg et al. (1960) and Stokes and Dawber (1959). The reason is obvious. Persons with painless infarcts are not hospitalized as often as others, because the infarcts are not diagnosed. It follows

from this that the cases of painless infarcts that are hospitalized must be of a particular variety they must be characterized by other symptoms, like cardiac decompensation, which make a patient seek medical advice. That they are not of the average variety is borne out by their high four week mortality in this series, — 50.0 per cent.

In chapter III I have attempted to calculate the frequency of clinically undetected infarction in Malmö by another means. The figures there indicate that it occurs much more often than in 6.6 per cent of cases.

## LENGTH OF TIME BEFORE HOSPITALIZATION

The time it takes before a person with myocardial infarction is hospitalized depends upon how large an area the hospital serves, the ambulance facilities available, the attitude of the population to hospitalization, and other circumstances. Differences in these respects from place to place account for some of the difference between the mortality rates in different series, for as will be shown later a great many patients die during the first day after the clinical onset of infarction.

The Medical Department of the Malmö General Hospital is only for citizens of Malmö, and it lies almost in the center of town, so the geographical circumstances tend to favor rapid hospitalization. Moreover it is the only hospital in the city and no time is lost by transferring the patients between different hospitals. Cases of

acute infarction are always admitted to the Department at once and before any others if there is a shortage of

Table 17 *Distribution of 1,541 Cases of First Infarct from 1935 Through 1954 by Length of Time Between Onset of Infarct and Hospitalization*

|                                   | No. of Patients | %     |
|-----------------------------------|-----------------|-------|
| Already in hospital on infarction | 77              | 5.0   |
| Admitted within 24 hours          | 932             | 61.5  |
| Admitted 24—48 hours afterward    | 194             | 12.6  |
| Admitted 48—72 hours afterward    | 64              | 4.2   |
| Admitted 72—96 hours afterward    | 61              | 4.0   |
| Admitted 5—31 days afterward      | 174             | 11.3  |
| Length of interval uncertain      | 59              | 3.8   |
| Total                             | 1,541           | 100.0 |

*Table 18. Distribution of 1,541 Cases of First Infarct from 1935 Through 1959 Into Different Intervals Between Onset of Infarct and Hospitalization, by Five Year Periods*

|           | Already in<br>Hospital on<br>Infarction | Admitted<br>Within<br>24 Hrs. | Admitted<br>24-48<br>Hrs. After | Admitted<br>on 48h to<br>21st Day After | Length of<br>Interval<br>Uncertain |
|-----------|---|-------------------------------|---------------------------------|---|------------------------------------|
| 1935-1939 | 5.0                                     | 51.8                          | 13.5                            | 13.5                                    | 16.2                               |
| 1940-1944 | 6.8                                     | 53.0                          | 20.5                            | 13.7                                    | 6.0                                |
| 1945-1949 | 7.8                                     | 61.7                          | 14.8                            | 10.5                                    | 5.4                                |
| 1950-1954 | 3.4                                     | 68.2                          | 16.3                            | 11.1                                    | 2.0                                |

beds. Consequently it may be assumed that the patients in the present series were hospitalized comparatively soon after their infarct.

The records did not always state exactly how long before admission the infarction had begun, but they contained sufficient data for study of the interval in 94.2 per cent of the cases of first infarcts from 1935 through 1954. Table 17 shows the length of time between the onset of the infarction and hospitalization in these 1,541 cases. It was assumed for this analysis, as elsewhere, that the infarction began when the patient began to get the symptoms used as a criterion of infarction. Table 17 also shows the number of cases in which it was impossible to establish the length of the interval.

Five per cent of the patients were in hospital when they got their infarct. This is a higher rate than can

be explained by chance: these patients had mostly been hospitalized for progressive anginal pain and other cardiac symptoms often because it was thought that infarction was imminent. The 5.8 per cent of the cases in which the length of the interval was uncertain were not all ones of atypical or silent infarction: the majority were put in this group because the records were hazy about the length of time elapsing between infarction and hospitalization.

Table 18 compares the different five years periods for length of time between the clinical signs of infarction and hospitalization. It is seen there that the proportion of cases admitted within 24 hours increased with the course of the years mainly at the cost of the proportion with an uncertain interval. Apart from this there was little difference from one five year period to another.

## DIFFERENT CLASSES OF INFARCT

It would be good to have an objective method of classifying infarction into different types for it would make it easier to compare series from different hospitals and to compare different

sections of the same series. Several authors have worked out systems of classification. The first to win recognition is probably that of Helander (1949). His system has been used in

several Scandinavian series, and I used a modification of it for the present series.

Other methods of classification have been accepted in wide circles. Russek et al. (1931) suggested dividing cases into good and poor risks. As poor risks they considered cases characterized by one or more of the following conditions: 1. previous myocardial infarction, 2. intractable pain, 3. severe degree or persistence of shock, 4. significant enlargement of the heart, 5. gallop rhythm, 6. congestive heart failure, 7. auricular fibrillation or flutter, ventricular tachycardia or intraventricular block, and 8. diabetic acidosis or other serious complicating disease. This system is good for comparing different sections of the same series, as Russek et al. used it for, but it is not good for comparing different series, for some of the items, especially 2 and 8 are hard to evaluate objectively.

Schnur (1953) suggested giving a different number of points to different signs and symptoms, from 40 points for shock to 10 points for conditions like infection of the urinary tract and emphysema. He found that the mortality and number of points were closely correlated. This system was unsuitable for the present series as it was impossible to evaluate some of the items included in it from a study of old records.

After the data in the present material had been treated, Peel et al. (1962a) suggested another point system, taking into account age, sex, previous heart disease, shock, decompensation,

and electrocardiographic features associated with the infarct. This system, containing fewer items than Schnur's, leaves less scope for subjectivity.

## DESCRIPTION OF CLASSIFICATION USED

I divided my cases into six classes. The first three correspond to Hellander's (1949) groups.

*Mild* Electrocardiographic changes specific of myocardial infarction (Plotz, 1955) distinguishing the case from angina pectoris. No rise in the temperature, sedimentation rate or white blood count, or such a brief rise that it was not detected during hospitalization.

*Moderately Severe* Electrocardiographic changes specific of infarction. Rise in the temperature, sedimentation rate and white blood count.

*Severe* Besides the characteristics of the moderately severe class, a fall in blood pressure the first day after admission to below 100 systolic, or to less than two-thirds the usual pressure if the patient was hypertensive.

*Normal or Atypical ECG* Normal electrocardiograms or changes which do not permit the diagnosis of infarction, such as stationary abnormalities in ST or T or bundle branch block of uncertain duration. Otherwise symptoms and laboratory data typical of infarction.

*Not Detected Until Autopsy* This group was included to cover all the cases of acute infarction treated at the Department.

*Unclassifiable* Patients coming in

**Table 19 The 2 477 First Infarcts from 1935 Through 1959 Distributed by Class of Infarct and the Four Week Mortality in Each Class**

| Infarct Class              | No. of Cases | Per Cent of First Infarcts | No. of Deaths Within Four Weeks | Per Cent Four Week Mortality |
|----------------------------|--------------|----------------------------|---------------------------------|------------------------------|
| Severe                     | 384          | 15.5                       | 321                             | 83.6                         |
| Moderately severe          | 1,536        | 62.1                       | 364                             | 23.7                         |
| Mild                       | 85           | 3.4                        | 1                               | 1.2                          |
| Normal or typical ECG      | 183          | 7.4                        | 75                              | 41.0                         |
| Not detected until autopsy | 45           | 1.8                        | 40                              | 88.9                         |
| Unclassifiable             | 242          | 9.8                        | 57                              | 23.6                         |
| <b>Total</b>               | <b>2,477</b> | <b>100.0</b>               | <b>858</b>                      | <b>34.6</b>                  |

more than 72 hours after the onset of the infarct, without unequivocal history of shock, or indefinite laboratory data patients dying soon after admission, with only one ECG, if any autopsy evidence of infarct, but not enough laboratory data for classification.

Cases admitted more than 72 hours after the onset of the infarct were classed as moderately severe if they had an electrocardiogram pointing unequivocally to infarction and laboratory data compatible with infarct, but no history of shock.

#### DISTRIBUTION OF CLASSES AMONG FIRST INFARCTS

Table 19 shows the distribution of the 2 477 first infarcts in the six classes. As seen, 9.8 per cent could not be classified the mortality in this group 23.6 per cent, did not differ from that in the large, moderately severe group.

Only 88.9 per cent of the patients in whom the infarct was not detected until autopsy died within four weeks of their infarct. The remaining 11.1 per cent died after a longer interval.

In table 20 the number of mild, moderately severe and severe infarcts

**Table 20 Percentage of Severe, Moderately Severe and Mild Infarcts in Present Series of First Infarcts from 1935 Through 1959 and in Other Scandinavian Series and Four Week Mortality Rate in the Different Groups**

|  | Severe            |             | Moderately Severe |             | Mild              |             |
|--|-------------------|-------------|-------------------|-------------|-------------------|-------------|
|  | % of Whole Series | Mortality % | % of Whole Series | Mortality % | % of Whole Series | Mortality % |
| Helander 1949<br>(193 cases)               | 29.0              | 57.0        | 60.1              | 23.4        | 10.9              | 0           |
| Wallgren, 1950<br>(153 cases)              | 20.9              | 62.5        | 75.2              | 23.5        | 3.9               | 0           |
| Lindén, 1952<br>(512 cases)                | 43                | 71          | 42                | 35          | 15                | 6.5         |
| Helander and Lervander<br>1959 (206 cases) | 23.8              | 54          | 68.2              | 27          | 8.0               | 4           |
| Present series<br>(2,007 cases)            | 19.0              | 83.6        | 76.7              | 23.7        | 4.3               | 1.2         |

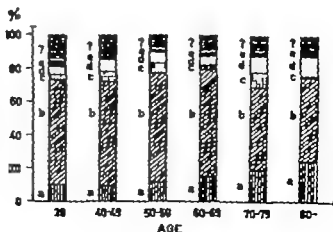
in the series is compared with the number in other Scandinavian series, divided according to the Helander system. The series are distributed about the same way in the three classes, except for Lindén's (1952) which contains more severe and mild infarcts and fewer moderately severe ones. It is not clear why his series differs in this way. It may be that some authors classify short, even momentary drops in blood pressure below the Helander limits as shock, and others not. I considered that shock was present when the blood pressure dropped below these limits for such a long time that measures were taken to counteract the drop or when the patient showed clinical signs of shock for any appreciable length of time. It may also depend on how many laboratory tests are made whether a case is classified as mild or moderately severe. If one uses a closely spaced series of tests routinely one probably detects laboratory signs

of infarction more easily than if one only uses a few tests.

The temperature was taken every day in each case of the present series and the sedimentation rate was determined several times in most of the cases. The white blood count was only determined once or twice shortly after the patient was admitted.

It is not possible to compare the mortality in the different groups in the present series with that in the others, for none of the others have a group corresponding to mine with a normal or atypical ECG. There should be a group of this kind if one is to keep strictly to Helander's criterion of a typical infarction ECG, for myocardial infarction is not always accompanied by typical electrocardiographic changes. Grewin (1956) said that they were lacking in every third case, which is much more often than in this series, where they were lacking in 7.4 per cent. Wahlberg (1963) said that the electrocardiograms were con-

Fig. 18. Percentage distribution of 2477 patients with first infarcts from 1933 through 1959 according to class of infarct. a = severe, b = moderately severe, c = mild, d = normal or atypical ECG, e = not detected until autopsy, f = unclassifiable.





sistent with acute myocardial infarction in only 87 per cent of his series. Eighty-one per cent of the present patients had severe, moderately severe or mild infarcts, and all these had electrocardiograms consistent with infarction.

In figure 16 each age group is subgrouped according to class of infarct.

### LABORATORY DATA

A number of laboratory data are reported to be of diagnostic or prognostic significance in the acute stage of myocardial infarction, i.e., the white blood count, eosinophil count, blood sugar, temperature, erythrocyte sedimentation rate and glutamic oxaloacetic transaminase in the serum (SGO-T). I used the cases of first infarcts from 1935 through 1954 for studying the white blood count, blood sugar, temperature and sedimentation rate. For studying the serum transaminase (SGO-T) I used the cases from 1935 through 1959 as well as 78 cases from a separate study in 1962. For studying the eosinophil count, and the correlation between different laboratory values, I used a series from 1961 and 1962 mainly compiled to study the effect of steroid therapy (chap. 4).

Whenever the records stated that the patients had an intercurrent disease which might have affected the laboratory data, I excluded them from the analysis, and also all the cases in which the records did not contain enough laboratory data. For the study

The percentage of severe infarcts increased highly significantly with advancing age. Otherwise there were no significant differences between patients of different ages, or any distinct trends towards a difference. The sexes were combined in this figure as they did not differ in this respect.

of the white blood count, blood sugar and temperature in the 1935—1954 series, I excluded the patients who died within 24 hours after the first clinical manifestation of infarction, and for the study of the sedimentation rate the patients who died within 72 hours.

### WHITE BLOOD COUNT

Data were available about the white blood count for 943 or 61.2 per cent, of the cases of first infarct from 1935 through 1954. Figure 17 shows how these cases were distributed by maximum white blood count and the number in each group dying within four weeks. As seen, the proportion dying within four weeks rose with a rise in the peak white blood count, the correlation between the white blood count and four week mortality being highly significant.

The sexes did not differ in this respect. Analysis of cases from 1961 and 1962 showed no correlation between age and the peak white blood count (118 pairs of tests,  $r = -0.10$ ).

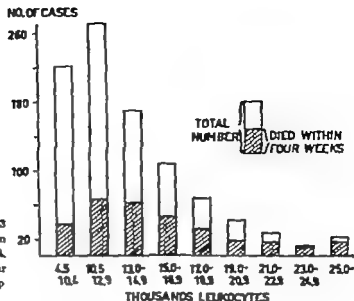


Fig. 17 Distribution of 943 cases of first infarct from 1933 through 1934 by peak white blood count and four week mortality in each group

Thus the greater mortality associated with a high white blood count, which Shillito et al. (1942) Brabme and Ahlberg (1947) Billings et al. (1949) Lindén (1950) Wright et al. (1954)

and others have observed is not a function of the greater mortality with advancing age.

Figure 18 shows the day on which the white blood count reached its peak in half the cases it did so within 24 hours and in every case within the first seven days. Yater et al. (1948) found that 60 per cent reached the peak within 24 hours and 84 per cent within two days.

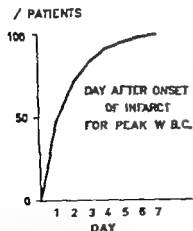
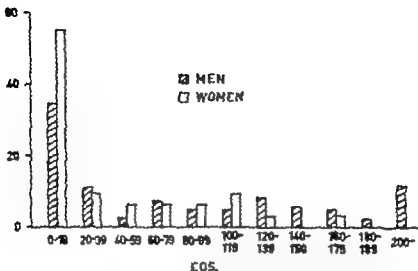


Fig. 18. Day after onset of infarct for peak white blood count in 943 cases of first infarct from 1933 through 1934

#### EOSINOPHIL COUNT

Most of Forsman's (1954) patients, or 56 per cent, had their lowest eosinophil count during the first 24 hours. Figure 10 shows the eosinophil count within 24 hours of the clinical onset of the infarction in 112 of my cases from 1961 and 1962, 81 men and 31 women (chap. 4) Forty per cent had counts below 20 and 51 per cent

## % PATIENTS



EOS.

Fig. 19 Percentage distribution of 81 men and 31 women from 1961 and 1963 by minimum eosinophil count within 24 hours of the clinical onset of infarction.

counts below 40. The women had lower counts than the men; the same was true in Forsman's series. There was a probably significant negative correlation between the eosinophil level and the age of the patient on infarction ( $r = -0.23$ ).

## BLOOD SUGAR

Figure 20 shows 744 cases of first infarcts from 1935 through 1954 grouped by peak blood sugar and the four week mortality in each group. None of these 744 had diabetes. There was a highly significant correlation between the peak blood sugar and mortality in both sexes. The women had higher peak values than the men.

In 53.8 per cent of the cases, the peak was reached within 24 hours, in

72.5 per cent within 48 hours and in 82.9 per cent within three days of the clinical onset of the infarct.

## NO. OF CASES

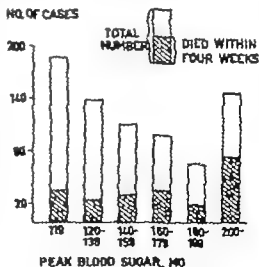
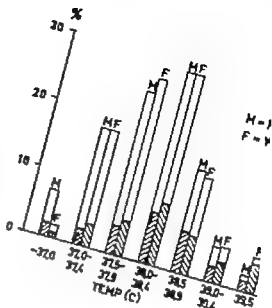


Fig. 20. Distribution of 744 cases of first infarct from 1935 through 1954 by peak blood sugar and four week mortality in each group.

Fig. 21 Percentage distribution of 893 cases of first infarct from 1923 through 1954 by highest rectal temperature in the morning and four week mortality in each group.



#### TEMPERATURE

Figure 21 shows 893 cases grouped by their highest rectal temperature in the morning and the four week mortality in each group. There is a highly significant correlation between the peak temperature and mortality. Bolling et al. (1949) and other authors have noted this correlation, while others including Ekelund (1951) and Lindén (1952) have said that it does not exist.

The peak temperature was not correlated with the age of the patient (table 22). The women tended to have higher temperatures than the men, but the difference was not significant.

Thirty five per cent of the patients had their highest temperatures within 24 hours, 57 per cent within 48 hours and 70 per cent within 72 hours. The corresponding figures in Forssman's (1954) series were 14, 64 and 90 per cent.

#### ERYTHROCYTE SEDIMENTATION RATE

Table 21 shows 594 cases grouped according to peak sedimentation rate and the mortality in each group. I excluded the patients dying before the fourth day from this analysis, as the rate generally does not reach its peak until after the third day. Plotz (1957) for example, said that the rate seldom reaches its peak until 24 hours after infarction, but almost invariably within 72 hours, and generally after 48 hours. I also excluded the cases with rates over 20 mm. per hour the first day as it was possible that the rate was high before the infarction started. The mortality showed no relation to the rate in either sex; there were no statistically significant differences. The women showed a greater mortality in all the groups; this was probably because they were older. Cases from 1961 and 1962 showed no



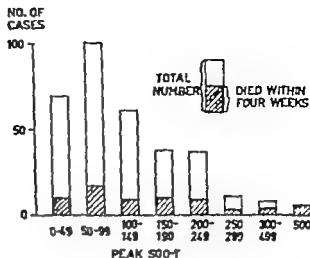


Fig. 23. Distribution of 330 cases of first infarct from 1955 through 1959 by peak SGO-T and four week mortality in each group.

special study in 1962 of 28 cases of acute myocardial infarction coming to the Department in which there was no doubt about the time of onset Figure 22 shows the mean values for the SGO-T on different days after these infarcts and also the range of these values. The highest values were obtained the second day after the infarct, which agrees with the observations of LaDue and Wróblewski (1955). The values were also high the third day.

There were 330 cases from 1955 through 1959 in which the SGO-T was measured on the second or third day after the infarct. Figure 23 shows the cases grouped by the peak values obtained, and the four week mortality in each group. There is a statistically significant correlation between the peak value for SGO-T and the mortality.

As seen from table 22 the cases from 1961 and 1962 showed a negative correlation between age and peak

SGO-T though it was not statistically significant ( $r = -0.16$ , 112 pairs of tests). If the amount of the rise in the SGO-T corresponds to the size of the infarct it follows from the correlation observed between the SGO-T and four week mortality that the four week mortality increases with the size of the infarct. Moreover it follows from the tendency to a negative correlation between the peak SGO-T and age that the correlation between the peak value for SGO-T and the four week mortality is independent of age.

#### CORRELATION WITH AGE

Table 22 shows the correlation between the laboratory data and age in the cases from 1961 and 1962. The tendency throughout is to a negative correlation, though the only correlation of note is the probably significant negative one between the eosinophil count and age. Nevertheless, the con

Table 22. *Correlation Between Laboratory Data and Age in 1961—1962 Series*

| Age               | V. D. C. | S. R. | SGO-T | Eosinophils | Temp. |
|-------------------|----------|-------|-------|-------------|-------|
| No. of test pairs | —0.10    | 0.00  | —0.16 | —0.23       | —0.08 |
|                   | 116      | 109   | 112   | 112         | 106   |

clusion seems to be justified that old patients tend to have less vigorous laboratory reactions.

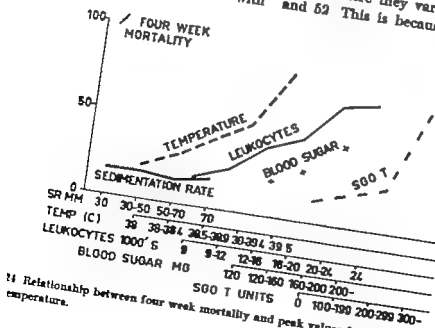
#### CORRELATION WITH FOUR WEEK MORTALITY

Figure 24 shows the correlation between the laboratory data and the four week mortality. Data were not analyzed for the eosinophil count in the cases from 1935 through 1959 and so no curve could be constructed for this value. The figure shows that the mortality rises with a rise in the temperature, white blood count, blood sugar and SGO-T but not with a rise in the sedimentation rate. In the cases from 1961 and 1962 treated with

placebo the average value for eosinophils within 24 hours was 15.7 for the women who died and 53.2 for the corresponding men. Table 31 shows that the mean values for the entire group including survivors, are 59.5 and 91.0 respectively. Thus it would seem that the mortality also rises with a decrease in the eosinophil count.

#### INTERCORRELATION

Table 23 shows the correlation between different laboratory data in cases from the 1961—1962 series. The number of test pairs varied between 103 and 116, except for the eosinophil count, where they varied between 50 and 52. This is because half the pa-



24 Relationship between four week mortality and peak values for four laboratory tests temperature.

tients were given steroids. As will be shown in chapter 4 the eosinophil count was the only laboratory value affected by the steroids administered. Consequently only the values for the patients given a placebo are included in this table.

Table 23 *Correlation Between Laboratory Data in 1961—1962 Series*

|          |     |     |     |   |
|----------|-----|-----|-----|---|
| Temp.    | +++ |     |     |   |
| W. B. C. | -   | ++  |     |   |
| Eos.     | -   | -   | (±) |   |
| S. R.    | +++ | +++ | -   | - |

SGO-T Temp. W. B. C. Eos.

- = \statistically significant correlation.  
 + = Probably significant correlation ( $0.05 > p > 0.01$ )  
 ++ = Significant correlation ( $0.01 > p > 0.001$ )  
 +++ = Highly significant correlation ( $p < 0.001$ )  
 (-) = Negative correlation.

To summarize the observations made in the foregoing analyses the higher the rise in the white blood count, blood sugar temperature and peak SGO T the higher was the four week mortality the eosinophil count showed a tendency to the same relationship the height of the sedimentation rate was not correlated with

the four week mortality there was a consistent tendency to a negative correlation between age at infarction and the intensity of the laboratory reactions after its onset as the four week mortality rises with age, this would indicate that the correlations between laboratory reactions and four week mortality are actually stronger than the ones observed.

The correlations between the different laboratory values shown in table 23 are confusing in some respects. The sedimentation rate, SGO-T and temperature were closely and positively correlated. The white blood count, on the other hand, was correlated positively with the temperature and negatively (probably significantly) with the eosinophil count but was not correlated in any way with the SGO-T or sedimentation rate. As mentioned, there is reason to believe that the rise in the SGO T is directly correlated with the amount of myocardial necrosis. Several studies indicate that the leukocytosis and rise in temperature are caused by the release of toxic substances from the infarcted area (Forsman, 1954) It is hard to understand, therefore, why the leukocytosis is not more closely correlated with the SGO-T and temperature.



## TREATMENT GIVEN PRESENT SERIES

## GENERAL MEDICAL TREATMENT

I made a detailed study of the drugs and other forms of general medical treatment given to a sample of 150 patients with first infarcts from 1935 through 1959. These 150 were representative of the cases of first infarcts from these years in regard to the year of the infarct, the age and sex of the patient and the class of infarct. Otherwise they were selected at random. The results aim to give a more comprehensive picture of the material used for the present study. I have not attempted to analyze the effect of this general treatment; the old hospital records were not suitable for this.

*Bed Rest*

In 136 of the 150 cases, or 91 per cent, it was recorded how long the patient stayed in bed. Figure 25 shows these 136 grouped by length of bed rest. With the passage of the 25 years, the length of the bed rest tended to grow shorter and shorter thus toward the end, between 1935 and 1959 as many as 33 per cent stayed in bed less than three weeks while 48 per cent stayed in bed between 3 and 6 weeks, and 19 per cent for more than 6 weeks, the same as in other years.

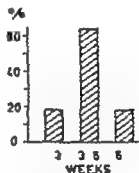


Fig. 25. Percentage distribution of 150 cases of first infarct from 1935 through 1959 by week of bed rest after infarct.

*Sedatives*

Eighty-eight per cent of the sample got barbiturates, chloral, meprobramate and compounds having a similar action. During the last five years, all the patients got drugs of this kind.

*Analgesics*

Eighty-one per cent of the patients got analgesics like morphine; the percentage remained practically unchanged throughout the 25 years.

*Vasodilators*

During the first 15 years 47 per cent of the patients got vasodilating agents, chiefly nitroglycerin, during 1950 to

1954 only 27 per cent and during 1955 to 1959 33 per cent

### *Oxygen*

Judging by the records, no oxygen was given until 1945. From 1945 to 1959 inclusive, between 15 and 20 per cent of the patients got oxygen, 17 per cent on the average.

### *Vasopressor Drugs*

During the first 15 years, 18 per cent of the patients got vasopressor drugs like ephedrine, from 1930 to 1954 only 8 per cent and from 1955 to 1959 none at all. During the last ten years nor epinephrine was prescribed more and

more for 5 per cent during 1950 to 1951 and for 13 per cent during 1955 to 1959

To sum up the length of the bed rest grew slightly shorter with the passage of the years the patients were given more and more sedatives, but the percentage given analgesics remained unchanged they got less and less vasodilating agents, finally only a third of them they got no oxygen the first fifteen years but the last ten years about every fifth of them did. The most distinct change with the years was the gradual replacement of drugs like ephedrine with nor epinephrine

## ANTICOAGULANT THERAPY

A large amount of research has been done on the efficacy of anticoagulant therapy for treating acute myocardial infarction, but the results vary. One of the first major studies was that of Wright et al. (1954) they reported the results of a study of 1 031 patients, some given anticoagulants and some not, depending on the date they were admitted. 16.0 per cent of the patients given anticoagulant therapy died soon after infarction, as opposed to 23.4 per cent of the others. They assumed that the lower short term mortality in the treated series was primarily due to the medicine having prevented fatal thromboembolic complications. A number of later authors confirmed that anticoagulant therapy reduced the number of thromboembolic complications and short term mortality

though some observed that also it increased the number of hemorrhagic complications, including cardiac rupture (Garb 1955). Others, including Eastman et al (1957) and Honey and Truelove (1957) did not observe a significantly better outcome after anti coagulant therapy. Hilden et al (1961) studying 800 cases concluded that routine treatment with anticoagulants did not reduce the mortality enough to justify its use. Their report led to an animated debate on problems of methodology principally in the Lancet in 1961 and 1962. Reports since then, by Pezold (1962) for example, have stated that anticoagulant therapy reduces the total mortality.

To sum up, there is still a great difference in opinion on whether anticoagulants are of any benefit in the

acute stage of myocardial infarction (Editorial in Brit. Med. J., 1962) It seems to be generally agreed that it reduces the number of thromboembolic complications but it is not yet established whether this advantage outweighs the increased risk of hemorrhage and cardiac rupture associated with this form of treatment

We began using Dicumarol in our Department in 1948, and started using it routinely a year or so later Thus no patient with myocardial infarction got this medicine before 1948 and practically every patient afterwards (Heparin was only used during 1950 to 1953 and then in only a few cases, and so it cannot have had any material effect on the results in the present series.)

Because of the statistical risks of a before-and-after study I did not attempt to determine the effect of Dicumarol on the total mortality in the present series Nor did I try to

determine the rate of thromboembolic complications If the records said nothing about complications it did not follow that they did not occur On the other hand, I studied the frequency of cardiac rupture in the series Altogether 94.5 per cent of the patients with a first infarct from 1935 through 1959 who died were autopsied, which is a high percentage compared to most other series. Cardiac rupture, with hemopericardium and cardiac tamponade, was observed in 104 out of the 811 autopsies. The age and sex distribution in the 104 and 811 cases are seen in table 54 in chapter 8.

Table 24 illustrates how often cardiac rupture was found on autopsy after anticoagulant therapy and other wise. The patients used for this analysis were all in hospital and alive 24 hours after the first clinical sign of infarction. As seen, the patients treated with anticoagulants had more ruptures than the others, even when one

*Table 24 Relationship Between Anticoagulant Therapy and Frequency of Cardiac Rupture as Shown by 333 Autopsies of Patients with First Infarcts During 1935 Through 1959 All in Hospital and Alive 24 Hours After Infarction but Dead within Four Weeks, 197 Given and 136 Not Given Anticoagulant Therapy*

|                                 | 2nd-3rd<br>Day | 4th-6th<br>Day | Dead on<br>6th-7th<br>Day | 7th-9th<br>Day | Total | Total<br>Estimated<br>Deaths<br>2nd-3rd<br>Day |
|---------------------------------|----------------|----------------|---------------------------|----------------|-------|--|
| <i>Given anticoagulant</i>      |                |                |                           |                |       |  |
| No. of autopsies                | 57             | 29             | 23                        | 88             | 197   | 140  |
| No. of ruptures                 | 9              | 5              | 3                         | 7              | 24    | 15   |
| % ruptures                      | 15.8           | 17.2           | 13.0                      | 8.0            | 12.2  | 10.7   |
| <i>Not given ant. coagulant</i> |                |                |                           |                |       |  |
| No. of autopsies                | 40             | 20             | 15                        | 61             | 136   | 06   |
| No. of ruptures                 | 5              | 2              | —                         | 5              | 12    | 7  |
| % ruptures                      | 12.5           | 10.0           | 0.0                       | 8.2            | 8.8   | 7.3  |

excludes the deaths on the second or third day to be sure the Dicumarol had had time to make its influence felt. The differences were not significant, however. Moreover as will be seen in chapter 8 the frequency of rupture is closely correlated with the age at infarction. The mean age of the patients with a first infarct increased during the course of the 25 years (chap 2) so part of the reason for the greater frequency of rupture among the patients given Dicumarol may be that they are all from the last ten years.

Thus these observations do not support the opinion of Wright et al. (1934) Waldron et al. (1934) Aarseth and Lange (1938) Lange and Aarseth (1938) and Capeel and Levy (1959) that cardiac rupture is more apt to occur after anticoagulant therapy than otherwise. They agree more with the observation of

Hilden et al. (1961) who did not find any statistical difference between treated and untreated cases.

Wright et al. (1934) and Hotten (1935) pointed out how misleading it might be to compare the rate of rupture found on the autopsy of patients given and not given anticoagulant therapy. As they said if anticoagulants reduced the deaths due to thromboembolic complications, this in itself would increase the proportion of deaths due to ruptures in autopsies. I.e. a greater proportion of deaths due to rupture after anticoagulant therapy did not have to mean that anticoagulant therapy increased the risk of rupture. This could not have been a large source of error in the present series, however for the proportion of ruptures per case admitted did not change from year to year (table 56 in chap 8).

## ADRENOCORTICAL STEROID THERAPY

There are four reasons why steroids might be useful for treating acute myocardial infarction.

- 1 They might increase the collateral circulation and reduce the final infarct scar. Studies of experimentally produced infarcts in dogs (Johnson et al., 1953) indicate that they do this, even though some authors, including Opdyke et al. (1953) say that they do not.

- 2 Steroids are reported to prevent various forms of disorders in rhythm

and conduction (Giraud et al. 1959; Zammit Maempel 1960; Peel and Dall, 1962b and others). Many of the early deaths after infarction are caused by these disorders, particularly ventricular fibrillation or asystole (Hellerstein and Turell, 1958; Wood, 1950) though the rates given range between 14 and 98 per cent (Imperial et al., 1960).

- 3 They are said to enhance the effect of the pressor substances currently used for shock in connection

with myocardial infarction, and also said to help prevent shock (Kaiser 1960)

4 They are said to reduce the systemic reaction to the toxic products of cellular disintegration and thus to reduce the amount of fever after infarction, among other things (Giraud et al., 1959)

Steroid therapy may also have its risks. Thus it may delay or impair the healing of an infarct and increase the risk of rupture in the acute phase. Experimental studies indicate that it does not (Chapman et al., 1952 Hoover and Manning 1954)

Several studies have been made on humans treated with steroids, (Bertola and Catelli, 1958 Gerisch and Campeau, 1958 Giraud, 1958 Giraud et al., 1959 Zammit Maempel, 1960 Gerisch et al., 1961) but up to the report of Peel and Dall (1962 b) the series have been small and not compared with proper control material. Peel and Dall (1962 b) made their study in Scotland at the same time as I was doing this investigation in Malmö, and got essentially the same results as I did.

I tried to get an answer to four questions Does steroid therapy affect the mortality? Does it affect the rate of disorders of cardiac rhythm or conduction Does it affect the rate of cardiac rupture? Does it affect the laboratory data

#### MATERIAL AND METHODS

A double blind study was done with patients admitted to the Department

from September of 1961 through February of 1962. During this period, every patient whom the receiving physician gave the presumptive or conclusive diagnosis of myocardial infarction of no more than 24 hours standing was given a medicine bottle containing either prednisone tablets of 5 mg. or placebo tablets of the same taste and color (both kindly supplied by A/B Ferring, Malmö) The bottles were marked only with a code number and as long as the patients were in hospital, no one knew which bottles contained prednisone and which ones the placebo During the first three days, the patients were given 30 mg. of prednisone or placebo a day during the fourth to sixth day 20 mg a day during the seventh to ninth day 10 mg. a day and during the tenth to twelfth day 5 mg a day.

Because it is sometimes impossible to make the diagnosis of infarction until the patient has been in the hospital a few days, it was necessary to give the tablets even on suspicion of infarction later on some of these patients had to be excluded. To get as homogeneous material as possible I excluded the patients admitted in shock. In 13 cases, shock developed after the patient had begun taking the tablets these were not excluded. Two patients with signs of simultaneous duodenal ulcer which might have reacted unfavorably to the steroids were excluded.

Table 25 shows how the cases for this study were collected. Table 26 shows the age and sex distribution in all the cases diagnosed as myocardial

**Table 25. Source of Six Month Material Used for Studying Effect of Steroid Treatment on Myocardial Infarction**

|   |     |  |
|---|-----|--|
| <i>Cases Used for Studying Steroid Treatment</i>                |     |  |
| Given steroid   | 61  |  |
| Given placebo   | 68  |  |
| Total   | 132 |  |
| <i>Of These the Following Died within 24 Hours of Admission</i> |     |  |
| Given steroid   | 3   |  |
| Given placebo   | 4   |  |
| Total   | 6   |  |
| <i>Cases from Same Six Months Not Included in Analysis</i>      |     |  |
| Admitted in shock   | 15  |  |
| Original diagnosis of myocardial infarction proved wrong        | 12  |  |
| Had ulcer as well   | 2   |  |
| Total excluded cases  | 29  |  |
| Total Number of Infarct During the Six Months                   | 161 |  |

infarction during the six months, in both the included and excluded cases. Only 18 per cent of the cases initially diagnosed as infarction during this

period were excluded from the study. The excluded patients were a little older on the average than the ones who were included, both the men and the women. This could be expected, for 15 of these 29 patients were excluded because of entering in shock, and the frequency of shock rises with age. The ratio of men to women was 2.6 to 1 for both the excluded and included patients.

The 132 included patients were tested routinely according to the scheme shown in table 27. In addition, the total need of anticoagulants (Dicumarol) during the first twelve days was noted. The patients were also used for the study of the correlation between different laboratory data and the correlation between these data and age (chap. 3). The laboratory tests were coded and multiple correlation coefficients calculated with a computer. The data were analyzed both for all 132 cases and for the four separate subgroups of men and women treated with steroids and placebo.

**Table 26. The Age and Sex Composition of the Cases Used and Not Used for the Study of Steroid Treatment in 161 Consecutive Cases of Myocardial Infarction from 1961 and 1962**

| Age       | Included in Steroid Study |       |      | Not Included in Steroid Study |       |      |
|-----------|---------------------------|-------|------|-------------------------------|-------|------|
|           | Men                       | Women | Both | Men                           | Women | Both |
| 30-39     | 2                         | —     | 2    | —                             | —     | —    |
| 40-49     | 16                        | —     | 16   | 1                             | —     | 1    |
| 50-59     | 15                        | 8     | 21   | 9                             | —     | 9    |
| 60-69     | 43                        | 8     | 51   | 7                             | 1     | 8    |
| 70-79     | 18                        | 17    | 35   | 2                             | 3     | 5    |
| 80 and on | 1                         | 0     | 7    | 2                             | 4     | 6    |
| Total     | 85                        | 27    | 132  | 21                            | 8     | 29   |
| Mean age  | 61.7                      | 72.0  | 61.6 | 62.6                          | 78.8  | 67.1 |

Table 27 *Testing Scheme Used in Each of 132 Cases from 1961 and 1962 Used for Study of Steroid Therapy*

| Test                 | 1         | 2 | 3 | 4 | 5 | 6 | 7 | 11 | 21 | 30 | 35 |
|----------------------|-----------|---|---|---|---|---|---|----|----|----|----|
| W.B.C.               |           |   |   |   |   |   |   |    |    |    |    |
| Blood sugar          |           |   |   |   |   |   |   |    |    |    |    |
| Eosinophil count     |           |   |   |   |   |   |   |    |    |    |    |
| Sedimentation rate   |           |   |   |   |   |   |   |    |    |    |    |
| Serum potassium      |           |   |   |   |   |   |   |    |    |    |    |
| Serum sodium         |           |   |   |   |   |   |   |    |    |    |    |
| Serum cholesterol    |           |   |   |   |   |   |   |    |    |    |    |
| 12 lead ECG          |           |   |   |   |   |   |   |    |    |    |    |
| Transaminase (SGO-T) |           |   |   |   |   |   |   |    |    |    |    |
| Temperature          | every day |   |   |   |   |   |   |    |    |    |    |
| Pulse                |           |   |   |   |   |   |   |    |    |    |    |
| Blood pressure       |           |   |   |   |   |   |   |    |    |    |    |

## EFFECTS OF TREATMENT

### Mortality

Table 28 shows the mortality within the first 12 days after infarction in the groups of patients treated with steroids and placebo. Two patients given steroids and 4 given the placebo

died before the end of the first 24 hours. These 6 were included as they were still alive 6 hours after they got the medicine, by which time it should have had a demonstrable effect (West, 1958).

Thirteen of the 51 patients receiv

Table 28. *Deaths Within 12 Day After Myocardial Infarct in 64 Patients Given Steroids and 68 Given Placebo*

| Age and Sex | Steroids        |        | Placebo         |        |
|-------------|-----------------|--------|-----------------|--------|
|             | Number of Cases | Deaths | Number of Cases | Deaths |
| Men         |                 |        |                 |        |
| 30-59       | 19              | 2      | 14              | —      |
| 60-69       | 18              | 4      | 25              | 3      |
| 70 and on   | 13              | 4      | 6               | 1      |
| Total       | 50              | 10     | 45              | 6      |
| Women       |                 |        |                 |        |
| 30-59       | 1               | —      | 5               | —      |
| 60-69       | 4               | 1      | 4               | 1      |
| 70 and on   | 9               | 2      | 14              | 4      |
| Total       | 14              | 3      | 23              | 5      |
| Both Sexes  |                 |        |                 |        |
| 30-59       | 20              | 2      | 19              | —      |
| 60-69       | 22              | 5      | 29              | 6      |
| 70 and on   | 22              | 6      | 20              | 5      |
| Grand Total | 64              | 13     | 68              | 11     |

ing steroids died, making a mortality of 20 per cent. Eleven of the 68 patients given the placebo died, making a mortality of 16 per cent. The difference is not significant.

It would seem from this table that the doses of steroids given in this study do not reduce the risk of death soon after the onset of myocardial infarction. Peel and Dall (1962 b) came to the same conclusion.

### *Disorders of Rhythm and Conduction*

Electrocardiograms being taken routinely on fixed days after the infarct it was possible to compare the frequency of disorders in cardiac rhythm and conduction in the steroid and placebo groups. Five patients suffered from disorders of rhythm or conduction, or both, before they got any tablets: 3 from left bundle branch block in one case combined with auricular fibrillation, and in another first degree atrioventricular block, 1 from right bundle branch block and 1 from auricular fibrillation.

Table 29 Occurrence of Ventricular Extrasystole Among 62 Patients Given Steroid and 64 Given Placebo

| Ventricular Extrasystoles        | Patients Given Steroids | Patients Given Placebo |
|----------------------------------|-------------------------|------------------------|
| Survivors                        | 16                      | 6                      |
| Dying within 12 day              | 3                       | —                      |
| Total                            | 19                      | 6                      |
| having ventricular extrasystoles | 29.0                    | 9.4                    |

Table 29 shows how many of the patients given steroids and the placebo had single or multiple ventricular extrasystoles. The steroid group showed

a statistically probably significant preponderance of these disorders. Table 30 shows that 7 patients had other forms of disorder in rhythm and conduction, 4 in the steroid and 3 in the placebo group. The six patients dying within 24 hours after infarction were excluded from table 29 and 30 since there was only one ECG for them and this was recorded before the steroid treatment was begun.

Thus the steroid therapy apparently did not help to prevent disorders of rhythm and conduction in this series. Dall (personal communication) is of the opinion that the steroids must be given in large doses parenterally to be of benefit: a team of Scottish investigators are now engaged in a study of this problem.

### *Frequency of Cardiac Rupture*

As mentioned, there is a theoretical possibility that steroid therapy increases the risk of cardiac rupture after infarction. Cardiac rupture occurs relatively seldom after myocardial infarction (chap. 8) but there were 2 cases of rupture with hemopericardium and tamponade in both the steroid and placebo group.

### *Laboratory Data*

Table 31 shows the mean values obtained in the laboratory tests for the men and women given steroids and placebo, and the mean values and standard deviations for the four groups combined. It also shows the number of tests on which each of the means was based. As the values were distributed about the same in the sub-



**Table 30 Disorders of Rhythm and Conduction Other Than Single Ventricular Extrasystoles Occurring Among 62 Cases Given Steroids and 64 Given Placebo**

|  | Patients Given Steroids<br>(— 62) |                         | Patients Given Placebo<br>(— 64) |                         |
|--|-----------------------------------|-------------------------|----------------------------------|-------------------------|
|  | No.                               | Dying Within<br>12 Days | No.                              | Dying Within<br>12 Days |
| Atrial fibrillation                    | 1                                 | 1                       | 1                                | —                       |
| Multiple ventricular extrasystoles     | —                                 | —                       | 1                                | —                       |
| Supraventricular tachycardia           | 1                                 | 1                       | 1                                | —                       |
| First degree atrioventricular<br>block | 2                                 | 1                       | —                                | —                       |
| Total                                  | 4                                 | 3                       | 3                                | —                       |

groups as in all the cases together the standard deviations are representative of the subgroups as well.

The white blood and eosinophil count the first day may be taken to indicate the severity of the infarction. These first day values were determined from specimens taken before any tablets were given. The men given steroids and placebo did not differ

significantly in the white blood and eosinophil count the first day but the women given steroids had a much lower eosinophil count than the women given placebo, the difference being highly significant. It would seem from this that the steroid group contained more cases of severe infarction than the placebo group another observation pointing to this is

**Table 31 Results of Laboratory Tests in Patients Given Steroids and Others Given Placebo Mean Values**

|                       | Men            |               | Women          |               | Total           |       |
|-----------------------|----------------|---------------|----------------|---------------|-----------------|-------|
|                       | Steroids       | Placebo       | Steroids       | Placebo       | Mean            | S.D.  |
| W.B.C., 1st day       | 11,310<br>(46) | 9,925<br>(39) | 10,975<br>(12) | 9,039<br>(19) | 10,530<br>(116) | 3,585 |
| Eos., 1st day         | 95.0<br>(44)   | 91.0<br>(37)  | 15.0<br>(12)   | 69.5<br>(19)  | 82.0<br>(112)   | 94.0  |
| SGO-T 2nd day         | 192.4<br>(44)  | 159.9<br>(39) | 159.5<br>(12)  | 122.4<br>(17) | 159.0<br>(112)  | 135.3 |
| S.R., 7th day         | 33.0<br>(43)   | 45.0<br>(36)  | 47.5<br>(11)   | 43.1<br>(19)  | 40.5<br>(100)   | 27.5  |
| Peak temp. first week | 37.78<br>(43)  | 38.00<br>(36) | 37.93<br>(10)  | 37.61<br>(17) | 37.83<br>(106)  | 0.62  |
| Pulse 2nd day         | 86.8<br>(48)   | 84.8<br>(40)  | 90.7<br>(12)   | 80.8<br>(18)  | 86.4<br>(115)   | 14.1  |
| Syst. B.P. 2nd day    | 137.0<br>(43)  | 133.6<br>(38) | 150.9<br>(12)  | 146.7<br>(18) | 138.0<br>(111)  | 24.5  |
| Diast. B.P. 2nd day   | 86.6<br>(43)   | 84.2<br>(38)  | 90.0<br>(12)   | 81.7<br>(18)  | 85.4<br>(111)   | 13.6  |

Figures in brackets denote number of patients tested.

Table 32. *Eosinophils and Serum Potassium and Sodium First Week After Onset of Infarction in Patients Given Steroids and Others Given Placebo*

|                 | Men           |               | Women         |               | Total          |       |
|-----------------|---------------|---------------|---------------|---------------|----------------|-------|
|                 | Steroids      | Placebo       | Steroids      | Placebo       | Mean           | S.D.  |
| Eosinophils     |               |               |               |               |                |       |
| 1st day         | 93.9<br>(11)  | 91.0<br>(37)  | 10<br>(12)    | 59.5<br>(19)  | 82.6<br>(112)  | 94.0  |
| 5th day         | 122.5<br>(43) | 216.5<br>(36) | 89.3<br>(16)  | 207.5<br>(17) | 173.3<br>(106) | 136.8 |
| Serum potassium |               |               |               |               |                |       |
| 1st day         | 4.55<br>(41)  | 4.52<br>(38)  | 4.11<br>(12)  | 4.43<br>(20)  | 4.47<br>(114)  | 0.51  |
| 7th day         | 4.19<br>(43)  | 4.52<br>(36)  | 4.26<br>(16)  | 4.28<br>(17)  | 4.35<br>(106)  | 0.46  |
| Serum sodium    |               |               |               |               |                |       |
| 1st day         | 139.9<br>(35) | 137.8<br>(31) | 138.5<br>(11) | 139.1<br>(14) | 138.8<br>(89)  | 3.4   |
| 7th day         | 139.9<br>(43) | 138.8<br>(36) | 140.1<br>(16) | 139.5<br>(17) | 139.5<br>(106) | 3.4   |

Figures in bracket denote number of patients tested.

that the steroid treated patients of both sexes had higher mean values for leukocytes than the others even if the differences were not significant.

After the first day there were no significant differences between the groups in laboratory values. One would have expected, especially from the report of Giraud et al. (1959) that the steroid therapy would have affected the temperature, and perhaps the sedimentation rate as well, but it did not.

It was interesting to see whether the steroids, which had no definite effect on the foregoing laboratory data, had been absorbed to an extent that affected biochemical values. Table 32 gives the amount of sodium and potassium in the serum the first and seventh day and the eosinophil counts on the first and fifth day.

Adrenocortical steroids having been

proven to favor the retention of sodium and excretion of potassium, one would expect the steroid and placebo cases to differ in the difference between the first and later values for these substances. One would also expect the same for the eosinophil count. As seen from table 32, they did differ for the eosinophil count. The difference was significant in men and even more so in women. The potassium values, on the other hand, showed a sex difference. For the men, they were the same in the steroid and placebo cases on the first day but highly significantly lower in the steroid cases on the seventh day. The women showed no significant difference. The sodium values did not change in any group.

The eosinophil counts were lower in all the groups on the first day than on the fifth, the difference being

greater than between the treated and untreated cases the fifth day. This would indicate that the strain associated with an infarct reduces the eosinophil count more than do the steroids administered orally. It also indicates that it may be because these patients got too small doses of steroids that their other laboratory reactions were not affected by the treatment. The lower first day values in the women than in the men indicates that the strain caused by the infarction led to greater reduction in eosinophils in them than it did in the men. It may be that the sex difference in potassium can be explained the same way.

#### *Dicumarol Need*

The men given steroids needed altogether 1.11 Gm. of Dicumarol during the first 12 days to reach a therapeutic index (measured according to Quick-Lehmann) while the men getting a placebo needed 1.30 Gm. The difference is statistically significant. The corresponding figures for the women were 1.06 and 1.19 Gm. While this difference was not significant, it showed the same trend.

#### *Summary*

To sum up the observations in this double blind study

The steroids in the doses they were given did not affect the mortality within the first 12 days after onset of infarction.

The patients treated with steroids had ventricular extrasystoles more often than the others but did not differ in other forms of disorders in rhythm or conduction.

There were 2 cases of cardiac rupture in each group.

The doses of steroids given the patients did not affect the white blood count, sedimentation rate, SGO-T or temperature. Nor did they affect the pulse rate or blood pressure.

There was a significant difference between the steroid and placebo cases in the drop in eosinophil counts, proving that physiologically active amounts of the orally administered steroids had been absorbed. The drop being even larger the first day after the infarct in both the treated and untreated patients, particularly the women, it would seem that the stress experienced by the patient on infarction caused a larger reduction in the eosinophils than did the orally administered steroids. The reason the steroids had no effect on other laboratory values, therefore, was probably that they had not been given in large enough quantities.

## INCIDENCE FROM YEAR TO YEAR

Before going on to the prognosis in myocardial infarction, I shall show how the hospitalized cases of this series were distributed over the twenty five years and discuss a number of the circumstances that might have affected the distribution.

Figure 26 shows the number of patients with infarcts admitted to the Department each of the 25 years under study the number of recurrent infarcts can also be seen there. It shows a successively greater number of cases with each year especially of men only about 28 patients were admitted per year in the 1930's, as against 235 in 1959 an almost ten fold increase. The study of cases from 1961 and 1962 (chap 4) indicated that the incidence went on rising after 1959. The question is was this rise in frequency from year to year due to a real increase in the incidence of the disease in Malmö, or was it due to other circumstances?

Figure 27 shows the rise in the incidence in Malmö from 1935 through 1959 compared with the rise shown by other Scandinavian series from about the same years.

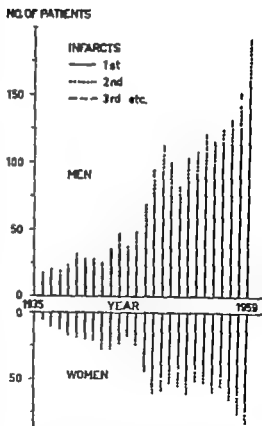


Fig 26. Number of men and women admitted for myocardial infarction to the Medical Department in Malmö each year from 1935 through 1959. Order of infarcts shown.

## NO. OF PATIENTS

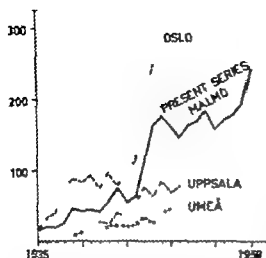


Fig. 27 Number of patients admitted for myocardial infarction in the present series and three other Scandinavian series from Oslo (*Acta med. scandinav. suppl.* 318 1966) from Uppsala (Lindén, 1953) and from Umeå (Ekvall, 1955)

Many others have noted a rise in the incidence of hospitalized cases of myocardial infarction. The rise is often attributed to a growing propor-

tion of old people in the general population and to improvement in diagnostic technique. Two other explanations are also possible: more hospital accommodation and patients being better able to pay for hospitalization.

#### CHANGE IN COMPOSITION OF UNDERLYING POPULATION

The population of Malmö rose from 141,485 in 1935 to 225,660 in 1959 and exact figures are available for the population every year in between. Of official statistics are available for the age and sex of the inhabitants in all the cities of Sweden they are only available for up to the age of 64 for Malmö, but it may be assumed that the age and sex distributions of the inhabitants of Malmö did not differ much from those of the other cities.

Table 33 shows the real figures for five year age groups from 30 to 64 inclusive, in Malmö and the figures for Malmö estimated from the com-

Table 33 Population of Malmö in 1951 Actual and Estimated by Age and Sex

| Age       | Men           |                   | Women         |                   | Both Sexes    |                   |
|-----------|---------------|-------------------|---------------|-------------------|---------------|-------------------|
|           | Exact Figures | Estimated Figures | Exact Figures | Estimated Figures | Exact Figures | Estimated Figures |
| 30—34     | 8,140         | 8,204             | 8,542         | 8,639             | 16,682        | 16,843            |
| 35—39     | 8,070         | 8,098             | 8,658         | 8,607             | 16,728        | 16,705            |
| 40—44     | 7,734         | 7,444             | 8,532         | 8,410             | 16,266        | 15,856            |
| 45—49     | 6,461         | 6,225             | 7,337         | 7,185             | 13,798        | 13,411            |
| 50—54     | 5,597         | 5,488             | 6,237         | 6,252             | 11,834        | 11,740            |
| 55—59     | 4,521         | 4,548             | 5,382         | 5,626             | 9,903         | 10,174            |
| 60—64     | 3,529         | 3,837             | 4,848         | 4,857             | 8,377         | 8,711             |
| 65—69     |               | 3,063             |               | 3,990             |               | 7,049             |
| 70—74     |               | 2,356             |               | 3,006             |               | 5,419             |
| 75—79     |               | 1,311             |               | 1,846             |               | 3,153             |
| 80—84     |               | 566               |               | 954               |               | 1,517             |
| 85—89     |               | 206               |               | 397               |               | 603               |
| 90 and on |               | 42                |               | 97                |               | 139               |

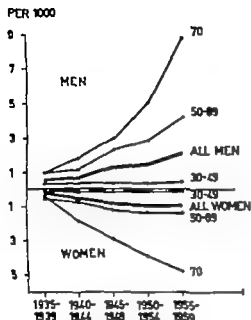


Fig. 28. Number of hospitalized first infarcts in men and women of different ages per 1,000 same-sexed, same-aged inhabitants of Malmö in different five year periods from 1935 through 1959

blined urban population as seen, the estimated figures come close to the real ones.

Figure 28 shows the change from one five year period to another in the number of patients hospitalized for myocardial infarction, this time expressed as the rate per thousand inhabitants of Malmö of the same age and sex. Thus even after correction for a change in the composition of the underlying population, the incidence of hospitalized infarcts rose steadily from year to year especially among old people.

In figure 29 the figures from the present series are compared with the

ones obtained from a similar analysis of 1 613 cases of myocardial infarction hospitalized during 1935 through 1949 in Oslo (Acta med. scandinav suppl. 315 1956) here the rates are given per 10 000 inhabitants and year. The results tally well

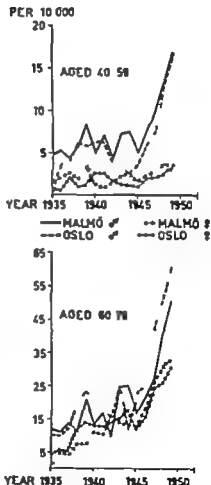


Fig. 29. Number of hospitalized first infarcts in men and women of different ages per 10,000 same-sexed, same-aged inhabitants of Malmö and Oslo (Acta med scandinav suppl. 315 1956) in different years from 1935 through 1949.

**Table 36 Yearly Means for Number of Available Beds in and Admissions to Medical Department of Malmö General Hospital from 1935 Through 1959 by Five Year Period**

| Five Year Period | No. of Beds (Mean) | No. of Beds Per 1,000 Inhabitants (Mean) | No. Admitted Per 1,000 Inhabitants and Year (Mean) | No. Admitted Per Year (Mean) | Mean Per Cent Bed Used |
|------------------|--------------------|--|--|------------------------------|------------------------|
| 1935—1939        | 150.0              | 1.01                                     | 2,197  | 14.8                         | 94.0                   |
| 1940—1944        | 161.5              | 1.00                                     | 2, 66  | 17.2                         | 104.5                  |
| 1945—1949        | 212.5              | 1.18                                     | 3,437  | 19.0                         | 94.8                   |
| 1950—1954        | 223.0              | 1.12                                     | 3,311  | 18.7                         | 89.1                   |
| 1955—1959        | 209.8              | 0.96                                     | 3,360  | 15.4                         | 89.8                   |

five year periods, and also these numbers in proportion to the number of inhabitants of Malmö. As seen, the number of beds varied little in proportion to the population of Malmö; there was no change here to explain the rise in the incidence of hospitalized cases of myocardial infarction. The number of cases admitted per thousand inhabitants also remained much the same. The high mean per cent of beds used during 1940 to 1944, the war years, was due mainly to a particularly high rate in 1941 to 1943 especially 1942. Unfortunately it is impossible to say what caused this. There was also an inexplicably high four week mortality during the war years, as will be seen in the next chapter.

#### CHANGE IN AMOUNT PEOPLE COULD AFFORD HOSPITALIZATION

Up through 1954, sickness insurance was voluntary in Sweden. At the beginning of the 25-year period 30 per cent of the inhabitants of Malmö were insured against sickness and during the first half of the 1950's about 46

per cent. Since 1955 every citizen of Sweden has been obliged to carry sickness insurance. This change can not have explained much of the rise in incidence of myocardial infarction, for even before 1955 hospital costs were defrayed mainly by public means. Persons belonging to a sickness benefit society got free hospital care, but ones who did not had only to pay the insignificant sum of three Swedish crowns a day.

Thus there was no major change in the ability of the people to pay for hospital care during the period in question. This is borne out by the observation in chapter 2 that occupation had no bearing on the four week mortality.

#### INFORMATION ON INCIDENCE FROM AUTOPSY DATA

The autopsy data proved to be of little use for explaining the rise in the incidence of hospitalized infarcts. It is true that 94.5 per cent of the patients with first infarcts were autopsied, but judging by figures from 1952 to 1954 only 39.5 per cent of all the inhabitants in Malmö who died at the

age of 30 or more were autopsied is long as the persons autopsied in hospital do not constitute a random sample of all the inhabitants who died, they cannot be used for calculating the real incidence of myocardial infarction.

Another way would be to study the frequency of healed infarcts found in all autopsies, not only of patients dying from myocardial infarction. Study of the autopsy records for the whole of Malmö during 1944 to 1951 in connection with the earlier investigations on part of the present material (Björck et al., 1957-1959) showed that the frequency of healed infarcts observed did not increase during these years. This would indicate that myocardial infarcts did not genuinely increase in incidence. But these autopsied patients constituted only a small and unrepresentative portion of the people dying in Malmö during these years. Furthermore, Söderström (1961) showed, after going through the autopsy records in Malmö from 1954 to 1959 that the number of healed infarcts noted in the records depended a great deal on how the autopsy was done and the way the pathologist

wrote his records. Thus it seems to be impossible to draw any conclusions about the incidence of infarcts from the available autopsy records.

To sum up it seems from the foregoing data and reasoning that a great deal of the rise in the incidence of hospitalized infarcts in Malmö, at any rate during the 1950s was due to a real rise in the incidence of infarction in the city during the 1930s and perhaps the 1940s the increase may be explained in other ways. The most probable source of error and the hardest one to evaluate is that the physicians were less apt to make the diagnosis of myocardial infarction at the beginning of the period than later.

A retrospective study of this kind is not suitable for explaining why so many authors have noted an increase in the 1940s and 1950s in the incidence of myocardial infarction and coronary heart disease. Mann (1957) after an extensive and critical survey of the reports on the increase in coronary heart disease, said that new epidemiologic data were needed from prospective studies of populations the same applies to myocardial infarction in particular.



## SHORT TERM OUTCOME

If one turns to the literature to see what risk a patient runs of dying within a few weeks of myocardial infarction, one meets with a wide variety of figures. Thus the figures given range from 20 per cent (e.g. Doscher and Poindexter 1950 and Reinfank et al., 1961) to about 50 per cent in some older studies (e.g. Levine, 1929 and Hochrein and Schneyer 1936). The figures for Sweden alone range from about 30 per cent (Helander 1949 Wallgren, 1950 Ekwall, 1955 Helander and Levander 1959 and Wahlberg 1963) to 55 per cent (Eckerström, 1951) with three series showing rates between 40 and 50 per cent (Ejrup and Nylin, 1943 Brahme and Ahlberg, 1947 Lindén, 1952). Most authors, however, seem to be agreed on a short term mortality around 30 per cent (Master et al., 1939 Rosenbaum and Levine, 1941 Miniz and Katz, 1947 Russek et al., 1951 Gillmann, 1955 Gorbатов 1961 and others) though slightly higher rates have been found in a few recent European series: 42.4 per cent in a series from Oslo (*Acta med. scandinav. suppl.* 315 1956) and 36.1 per cent for men and 45.4 per cent for women

in a series from Germany reported by Döring and Loddenkemper in 1962.

This large discrepancy in the figures for short term mortality is obviously due to differences in the composition of the various series. Thus the series differ in the ages of the patients they contain, and this makes a great difference to the mortality as will soon be shown. Secondly they differ in source, not all of them being representative of the population from which they come. Furthermore different authors use different lengths of time after the infarction for calculating the short term mortality. Many set the limit at four weeks after the first clinical manifestation of infarction, while others like Döring and Loddenkemper (1962) reckon with up to three and a half months afterward. Still others reckon with the time the patients are in hospital, but this naturally varies with the amount of hospital accommodation available and the local opinion on the best way to treat infarction. This method also has the disadvantage that patients kept on in hospital for other reasons and dying there, are included in the short term mortality for myocardial infarction.

even when the infarct for which they were initially hospitalized had healed long before they died.

In this series the short term mortality was judged from the death within four weeks of the clinical onset of the infarct. The present chapter deals with the four week mortality in the 2,477 cases of a first infarct.

### SEX AND AGE

The four week mortality in all 2,477 cases of a first infarct amounted to 34.6 per cent. 31.8 for the men and 37.5 for the women.

#### A FOUR WEEK MORTALITY

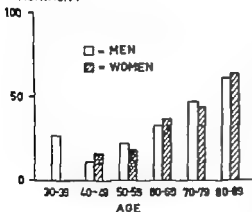


Fig. 30. Percentage four week mortality in 1,685 men and 863 women of different ages with first infarcts from 1955 through 1959

Figure 30 shows the four week mortality rate in different age and sex groups. The numbers of cases on which the percentages are based are seen in table 3. There were only 5

women between 30 and 39 and so there is no bar for them in figure 30 for that matter all 5 survived the first four weeks. There were also too few patients of 90 and over to be able to show them in figure 30—only 8, of whom 7 died within four weeks.

As seen, the mortality was high in the men between 30 and 39. After that age it dropped, and then rose steadily with an increase in age. The mortality for the patients in their 30's, 76.3 per cent, lay midway between the mortality for patients in their 50's and 60's. Others have observed a high mortality among young people but surprisingly little has been written about this in the literature. It is not agreed whether persons who get an infarct when they are extremely young have a worse outlook than older persons. McVay (1956) and Ikkala and Kalpalainen (1957) say they do not, but others have noted figures much like those in the present series. Döring and Loddenkemper (1962) collecting 18,055 cases of myocardial infarct from 69 hospitals in West Germany from the years 1948 through 1960 noted a mortality of 37.9 per cent in the 29 women under 40 and of 23.2 per cent in the 233 men under 40. This deviation in mortality in people under 40 is taken up in greater detail in chapter 10 together with other characteristics of the young patients in the present series.

As noted, the mortality was higher among the women than among the men, 37.5 as against 31.8 per cent. This was because the women were of older average age than the men when

they got their infarcts. After adjustment for age, their mortality amounted to 31.0 per cent, which is almost the same as the men's 31.8 per cent. Unless correction has been made for age, therefore, one cannot rely on reports (e.g. Zinn and Cooby 1950) that women are more apt to die from infarction than men. The present series does not allow conclusions concerning a sex difference in mortality in the youngest age group for it contained too few women. The series collected by Döring and Loddenkemper (1962) however indicates that the mortality is also high among young women.

#### SEVERITY OF INFARCT

Figure 16 showed that the proportion of mild and moderately severe infarcts changed slightly with advancing age in the present cases of first infarct, but the proportion of severe infarcts increased significantly with age. The question is, therefore, whether the rise in mortality with the severity of the infarction has less to do with the severity of the infarct than to the circumstance that the people getting severe infarcts are generally older. Figure 31 however shows that the four week mortality rises with an advance in age, whatever the class of the infarct. (The mortality was not calculated for the groups containing less than 10 patients.) The curve for the moderately severe infarcts in figure 31 is based on 1,630 patients, 24 between 30 and 39 and 123 between 40 and 49 as seen the mortality was unexpectedly high in the patients in

their 30's. Each of the curves takes the same course as the one in figure 30. Consequently the high mortality in the young patients was not due to their being prone to more severe forms of infarct.

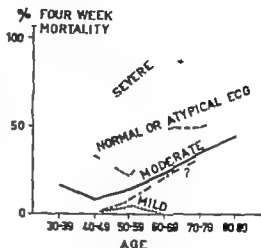


Fig. 31 Relationship between four week mortality and class of infarct in 2,468 cases of a first infarct from 1935 through 1939

#### CALANDER YEAR OF INFARCTION

Figure 32 shows the four week mortality in each of the 25 years under study (curve) and in five year periods (bars). The total mortality 34.6 per cent, is shown as a horizontal double line. The curve for the separate years goes up and down erratically except for the war years 1940 and 1941 when the mortality was significantly higher than in other years. The high rates these two years is reflected in the high bar from 1940 through 1944 during which period the four week mortality was statistically significantly in excess of that in the other five year periods. As already demonstrated age

Table 3 Age-adjusted Four Week Mortality Rate in 2,477 Cases of First Infarcts from 1935 Through 1959 by Sex and Five Year Period

| Five Year Period | No. of Cases | Men       |                | No. of Cases | Women     |                |
|------------------|--------------|-----------|----------------|--------------|-----------|----------------|
|                  |              | Mortality | Standard Error |              | Mortality | Standard Error |
| 1935-1939        | 93           | 33.7      | 4.9            | 49           | 54.9      | 7.2            |
| 1940-1944        | 142          | 43.2      | 4.2            | 91           | 42.0      | 5.1            |
| 1945-1949        | 298          | 36.6      | 2.8            | 191          | 29.8      | 3.3            |
| 1950-1954        | 423          | 27.2      | 2.2            | 240          | 33.6      | 3.0            |
| 1955-1959        | 633          | 29.7      | 1.8            | 303          | 42.2      | 2.8            |

has a large influence on the four week mortality Table 3 shows the mortality rates for the five year periods adjusted for age the sexes are shown separately here. As seen, even after this adjustment the men continued to show a higher mortality during the years 1940 to 1944 than in the other five year periods, while the rate for the women grew steadily lower during the first three periods, to rise again in the next two

years, the four week mortality for the women rose distinctly but not for the men. I have not been able to find any explanation for this. The figures for these years are more reliable than during the first ten years because of the relatively larger number of cases and the relatively little improvement in accuracy of diagnosis as compared with the first ten years (chap 5)

#### % FOUR WEEK MORTALITY

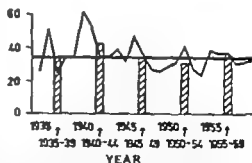


Fig. 22. Four week mortality per year (curve) and five year period (bars) in 2,477 cases of a first infarct from 1935 through 1959. The double horizontal line shows the four week mortality for the 2,477 cases combined.

It was impossible to determine why the men had a higher mortality during 1940 and 1941. Though Sweden was neutral in the second world war the difference in 1940 and 1941 was probably due to the war in some way. Perhaps it was caused by a difference in hospital facilities these years. This hypothesis is borne out by the larger number of beds used these years (chap 5). As long as this reason cannot be excluded, it is idle to speculate on whether the higher mortality was due to other factors operating during the years of the war.

Table 37 shows another surprising circumstance. During the last fifteen

## LONG TERM OUTCOME

## LONG TERM SURVIVAL

## MATERIAL AND METHODS

In most countries it is hard to study the long term outcome because it is impossible to track down patients several years after they were last seen, for example, in a hospital. This is easier in Sweden. Every inhabitant is kept track of in the parish registers. If one knows the names and birthdays of people, one can get hold of nearly all of them, even after many years, and even if they have moved several times. If they have died, the registers also state when.

Altogether 1 619 persons with first infarcts survived the first four weeks. Long range treatment with anticoagulants was only begun in 1957 in Malmö and then not routinely. Thus most of the 1 619 patients had not had anticoagulant therapy for any length of time only 30 patients were on anticoagulant therapy from the time they were discharged till they died or till the end of the follow up in 1962. These patients were excluded from the analysis of the long term results, leaving 1,589 cases. No more mention will be made of these 30 patients they were too few and were

not selected at random, and do not permit any conclusions of value about the influence of this therapy on the outcome.

Some patients were put on long range anticoagulant treatment not on their first infarct but later on, often after another infarct. These patients 109 in number were included up to the time they were started on the anticoagulant treatment, when they were withdrawn.

The data from the parish registers concerning the features under study were analyzed by the life table method, of which a brief description follows.

*Life Table Method Used*

A detailed description of the life table method is presented by Merrell and Shulman (1955). Another comprehensive and clear description is given by Cutler and Ederer (1958). I used the following technique.

I constructed the survival curve for each group by cumulatively multiplying the number of survivors at the beginning of a time interval ( $x$ ) by the probability of surviving this in

interval. This probability is based on the number of observed deaths during the interval in question. Thus,

$$1_{x+1} = (1-q)$$

when 1 is the proportion alive at the beginning of interval  $x$  and  $q$  is the probability of dying during the interval  $x$

The patients who left the series for another reason than death were treated as withdrawals ( $w$ ) most of them left because the period of observation was up, others because they began getting long range anticoagulant therapy and a few because they were lost to the study

The standard error of the survival curve was calculated from the formula

$$SE_{1_x} = \sqrt{\frac{\text{Sum of } \frac{q}{(1-q) \left(0 - \frac{n}{2}\right)}}{n}}$$

where 0 is the number of patients at the start of the interval  $x$ .

Thirty five of the 1,589 original patients could not be found for the follow up. Some of them were known to have left Sweden some had probably been given the wrong birthdate in the records. But the observations in the other 97.8 per cent could hardly have been biased by the lack of these few cases. They were all included in the follow up analysis, however. With the life table method every case is included until it can no longer be traced, when it is then treated as a withdrawal. Thus if a patient was known to be alive for six months, he or she was included in the life table during these six months. Though I did not

reckon the survival in six month intervals, a patient of this kind enhances the reliability of the survival figures even for periods longer than six months. All these 35 patients could be followed till at least the day they left hospital and some of them longer as they returned as outpatients for different lengths of time.

## RESULTS AND ANALYSIS

The 1,589 survivors correspond to 8 07 person years of experience 5 917 for the men and 2 760 for the women. Figure 33 shows the survival curves for the two sexes. It also shows the results of other authors for the sake of comparison. (For an extensive review of the literature on the subject the reader is referred to Master 1961). As seen the results vary greatly from series to series, the five year survival rates, for example, ranging from 12 to 67 per cent. There is not much point in comparing the results of different series, however. They vary greatly even in important characteristics like age and sex distribution, length of time covered by the short term mortality and whether or not they include reinfarcts. Nor are they all representative of a well defined total population.

### *Sex and Age at Infarct*

Figures 34 and 35 show the survival curves for the men and women divided by ten year age groups. As seen from figure 34 the older the men were at infarction the worse was their long term outcome. The men getting their infarcts in their 30's seemed to be an

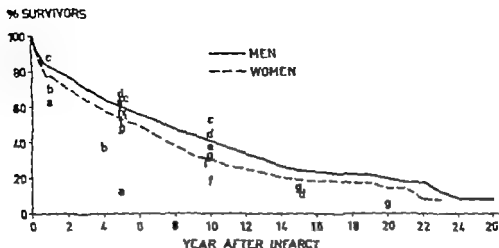


Fig. 23. Percentage of short term survivors still alive at different numbers of years after myocardial infarction. Curves = present series — Katz et al. (1949) b = Echerström (1951) c = Smith (1953) d = Cole et al. (1954) e = Weiss (1956) f = Olsen et al. (1956); g = Richards et al. (1956) h = Helander and Levander (1959); i = Joergens et al. (1960)

exception, however having a worse long term outcome than one would expect (the same as they had had an unexpectedly poor short term outcome). The women had a worse long term outcome with advancing age on

infarction, at least with ages of 40 on it was impossible to draw any conclusions about younger women, as there were only 6 in the series.

This is not the correct way to judge the effect of age at infarction on the

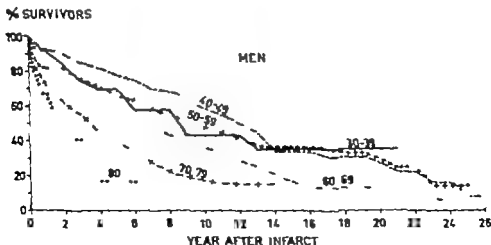


Fig. 24. Percentage survivors at different numbers of years after infarction in 1,020 four week survivors of different age on infarction. Men with first infarct.

## % SURVIVORS

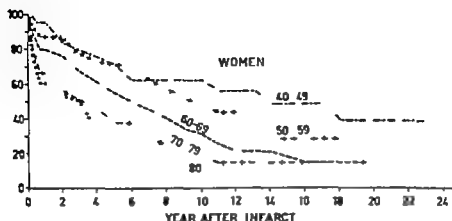


Fig 35. Percentage survivors 1 different numbers of years after infarction 1 545 four week survivors of different age on infarction. Women with first infarction.

long term outcome however though it is often used. It is better to compare the outcome in different age and sex groups with the outcome for persons of the same age and sex in the general population. This is easy to do in Swe-

den, because all the data are obtainable from the Official Statistics of Sweden.

Table 38 shows the number of deaths 5, 10, 15 and 20 years after the infarction in different age and sex

Table 38 Number of Deaths at Different Intervals After First Clinically Evident Infarction Among 1,584 Four Week Survivors from 1935 Through 1959 by Sex and Age at Infarction, Compared with Corresponding Numbers in General Population

| Age and Sex | No. of Patients | (Observed/Expected Deaths at Different Intervals After First Infarction) |         |          |          |          |
|-------------|-----------------|--|---------|----------|----------|----------|
|             |                 | 1 Year   | 5 Years | 10 Years | 15 Years | 20 Years |
| Men         |                 |  |         |          |          |          |
| 30-39       | 23              | 33.3   | 28.4    | 26.2     | 24.5     | 17.7     |
| 40-49       | 140             | 13.9   | 6.5     | 6.3      | 5.5      | 6.5      |
| 50-59       | 332             | 10.3   | 8.1     | 4.8      | 4.6      | 3.7      |
| 60-69       | 348             | 7.3  | 3.3     | 2.8      | 3.3      | 2.7      |
| 70-79       | 172             | 6.0  | 3.1     | 2.5      | —        | —        |
| 80 and over | 24              | 2.7  | 0.5     | —        | —        | —        |
| Women       |                 |  |         |          |          |          |
| 40-49       | 25              | 20.0   | 15.4    | 10.5     | 10.1     | 8.9      |
| 50-59       | 108             | 12.5   | 8.7     | 5.3      | 5.8      | 4.2      |
| 60-69       | 196             | 9.8  | 3.0     | 3.4      | 3.0      | —        |
| 70-79       | 180             | 8.0  | 3.1     | 2.6      | 2.0      | —        |
| 80 and over | 27              | 4.2  | 1.8     | —        | —        | —        |

There were only 5 women aged 30-39, and so they were excluded from this table



series consists of 979 patients with infarcts from the years 1935 through 1949 who left hospital alive. So as to make the Malmö series more comparable with this series, I took only cases from 1935 through 1954. I also excluded men under 40 and over 80 and women under 50 and over 80 as the Oslo study gave only a few ratios, if any for these ages. This left 907 patients in the Malmö series.

As seen in table 39 the two series differed somewhat in their figures for the 40 year old men. There were only 94 men of this age in the Malmö series and only 90 in the Oslo series, and so the difference was probably coincidental. Otherwise the ratios between the observed and expected death rates agree on the whole. The excess mortality was much greater the first year after hospitalization than later for every age group in both sexes. This tallies with the observation that the risk of recurrence after a first infarct is greatest during the year immediately following the infarct. As will be shown in chapter 9 this has already been demonstrated by Bjerkelund (1957) in a study of the effect of long range treatment with anticoagulants after myocardial infarction.

Figure 33 showed that the women in the present series had a worse long term outcome than the men when differences in age were disregarded. As demonstrated in chapter 2 however the women were older than the men at infarction and the outcome grows worse with an increase in age. Comparison with the mortality in the general population of the same age and

#### OBSERVED OVER EXPECTED DEATHS

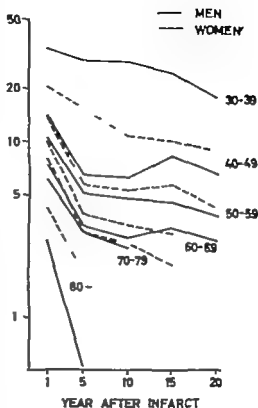


Fig. 38. The curves in figures 36 and 37 plotted with a logarithmic ordinate.

sex gives a better idea of how much the sexes differ in long term outlook.

In figure 38 the quotients derived from dividing the observed by the expected number of deaths used to construct figures 36 and 37 are presented with the ordinate constructed on a logarithmic scale to give a better picture. As seen there, the women had a slightly worse outcome than the men in every age group. The sex difference was not statistically significant in any of the separate age groups, but the

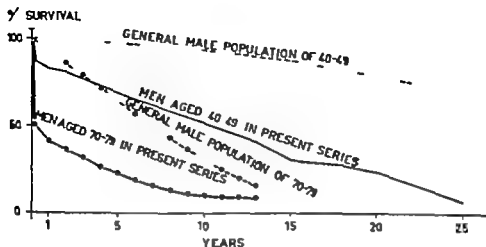


Fig. 39. Percentage survival at different times after admission for first infarct in men getting their infarct in the 40's and 70's and in men of corresponding ages in the general population.

tendency to a worse outcome for the women was so consistent that a larger series might very well reveal a small but significant difference between the sexes. Erkelens (1962) analyzed 924 patients from Rotterdam one third of them inpatients and two thirds outpatients. His series is not directly comparable with mine, as it does not appear to be fully representative of the population of Rotterdam. Analysis of his series, however, reveals that after adjustment for age, the two sexes showed about the same excess mortality.

Figure 39 gives a final illustration of the effects of age at infarction on the mortality. It shows the survival curves for the men in their 40's and 70's in the present series and in the general population of Malmö. These decades were the ones at either side of the age range containing enough cases to permit a reliable survival

curve. The decades in between gave curves between these two. Unlike the previous figures, figure 39 shows the mortality from the time of hospitalization onward not from the fifth week onward. The drop in the beginning of the curve, large for the men in the 70's and relatively small for the men in their 40's, reflects the four week mortality. (The difference between these ages in four week mortality was taken up in chapter 6.) After this initial drop the curves slope differently than the corresponding curves in figure 34 because in figure 39 100 per cent means all the hospitalized patients but in figure 34 only the patients discharged alive. Figure 39 shows, for example, that 60 per cent of the men in their 40's survived the first five years as against 23 per cent of the men in their 70's. After 10 years, the corresponding figures were 62 and 10 per cent.

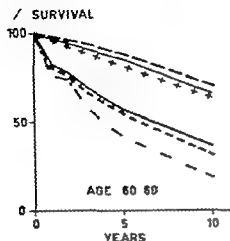


Fig. 41

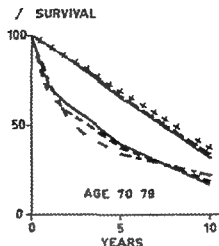


Fig. 42

comitant diabetes and myocardial infarction, including diagnostic criteria and short term outcome, the reader is referred to chapter 2.)

Figures 40-41 and 42 present the

survival curves for different diabetic and nondiabetic groups from the Malmö and Kristianstad series in the fifth, sixth and seventh decade. All three figures, particularly the ones for

Table 42. Comparison Between General Population and Present Series of First Infarct from 1935 Through 1954 for Differences in Long-Term Survival in Nondiabetics and Diabetics by Age

| Surv. After                                      | Quotient Derived by Dividing Percentage Survival in First Group with That in Second |       |       |
|--|---|-------|-------|
|  | Age   |       |       |
|  | 60-69   | 60-69 | 70-79 |
| <b>1 Year</b>                                    |   |       |       |
| Gen. pop./diabetics in gen. pop.                 | 1.02  | 1.02  | 1.00  |
| Whole present series/diabetics in present series | 1.13  | 1.03  | 0.92  |
| <b>2 Years</b>                                   |   |       |       |
| Gen. pop./diabetics in gen. pop.                 | 1.04  | 1.03  | 1.00  |
| Whole present series/diabetics in present series | 1.23  | 1.03  | 1.07  |
| <b>3 Years</b>                                   |   |       |       |
| Gen. pop./diabetics in gen. pop.                 | 1.07  | 1.03  | 0.90  |
| Whole present series/diabetics in present series | 1.38  | 1.17  | 1.18  |
| <b>5 Years</b>                                   |   |       |       |
| Gen. pop./diabetics in gen. pop.                 | 1.12  | 1.06  | 0.96  |
| Whole present series/diabetics in present series | 1.25  | 1.31  | 1.12  |
| <b>10 Years</b>                                  |   |       |       |
| Gen. pop./diabetics in gen. pop.                 | 1.26  | 1.07  | 0.90  |
| Whole present series/diabetics in present series | 1.22  | 1.26  | 0.80  |

the fifth and seventh decades indicate that the excess mortality attendant upon diabetes is about the same in both the general population and the infarct series.

Table 42 takes up the same data again with the sexes combined. It shows the quotients derived from dividing the percentage of diabetic and nondiabetic survivors at different times in the two series. As seen, the quotients are about the same everywhere though they are somewhat smaller in the general population than for the patients with infarcts. It would seem from this table that diabetic persons who have had an infarct have a long term excess mortality that is only insignificantly greater if any thing than the long term excess mortality attendant upon diabetes added to the long term excess mortality attendant upon infarction. In other words, the circumstance that the two disorders are combined does not in itself appear to make much difference to the outcome in the long run.

### Severity of Infarct

Several authors, including the Scandinavian authors Olsen et al. (1958) report that clinically severe infarction increases the risk of death even beyond the first few weeks as shown in chapter 3 the four week mortality is closely correlated with the severity of the infarct.

Table 43 shows the long term outcome of the four week survivors of first infarcts between 1935 through 1954 grouped by whether they had had mild, moderately severe or severe infarcts. The cases with a normal or atypical electrocardiogram are excluded from this analysis they include infarcts of different grades of severity (They showed practically the same survival rates as the moderately severe group) There the cases are divided only into those over and under 60, as there were too few mild and severe cases to warrant presentation in smaller age groups.

Table 44 was constructed to give a more easily grasped picture of the

Table 43. *Per Cent Survival at Different Numbers of Year After Infarction of the 743 Four Week Survivors with Mild Moderately Severe and Severe First Infarct During 1935 Through 1954 by Age at Infarction*

|                             | Person Years<br>Lived After<br>Infarct | Per Cent Alive After |         |         |         |          |          |
|-----------------------------|--|----------------------|---------|---------|---------|----------|----------|
|                             |  | 1 Year               | 2 Years | 3 Years | 5 Years | 10 Years | 15 Years |
| Under 60 at time of Infarct |  |                      |         |         |         |          |          |
| Severe Infarct              | 962                                    | 94.1                 | 82.4    | 70.3    | 76.3    | 51.4     |          |
| Moderately severe Infarct   | 1,690.3                                | 87.8                 | 83.3    | 77.2    | 63.5    | 42.4     | 12.5     |
| Mild Infarct                | 2120                                   | 90.2                 | 86.9    | 80.3    | 76.9    | 66.5     | 57.1     |
| 60 on at time of Infarct    |  |                      |         |         |         |          |          |
| Severe Infarct              | 61.2                                   | 66.2                 | 50.0    | 45.5    | 31.3    |          |          |
| Moderately severe Infarct   | 1,346.3                                | 74.8                 | 69.8    | 62.0    | 48.4    | 27.1     | 9.26     |
| Mild Infarct                | 87.6                                   | 82.4                 | 70.6    | 58.8    | 52.9    | 34.5     |          |

Table 44 Long Term Percentage Survival After Severe and Mild Infarcts Compared with Long-Term Survival After Moderately Severe Infarcts Same Cases as in Table 43

|                             | Quotient Obtained by Dividing % Survivors by % Survivors in Moderately Severe Group After |         |         |         |          |          |
|-----------------------------|---|---------|---------|---------|----------|----------|
|                             | 1 Year  | 2 Years | 3 Years | 5 Years | 10 Years | 15 Years |
| Under 60 at time of infarct |   |         |         |         |          |          |
| Severe infarct              | 1.07  | 0.99    | 0.99    | 1.16    | 1.21     |          |
| Moderately severe infarct   | 1   | 1       | 1       | 1       | 1        | 1        |
| Mild infarct                | 1.03  | 1.04    | 1.04    | 1.17    | 1.02     | 4.57     |
| 60 on at time of infarct    |   |         |         |         |          |          |
| Severe infarct              | 0.91  | 0.72    | 0.73    | 0.65    |          |          |
| Moderately severe infarct   | 1   | 1       | 1       | 1       | 1        | 1        |
| Mild infarct                | 1.10  | 1.01    | 0.93    | 1.09    | 1.27     |          |

relationship between the degree of clinical severity and the outcome. Here the percentage of survivors in the largest of the three groups, the moderately severe infarcts was taken as 1 and the percentage of survivors in the mild and severe groups shown in relation. As seen, the quotient for the mild group exceeded 1 at nearly every point of time after the infarction, indicating that these patients ran a smaller risk of dying in the long run than the patients with a moderately severe infarct. The severe group showed quotients below 1 for the most part, indicating that the prognosis is worse for them than for the moderately severe cases. The largest differences in the table those between severe and moderately severe cases 2 and 3 years after infarction in patients over 60 are probably significant. Otherwise, none of the differences are statistically significant.

Thus the present series indicates that the chances of long term survival are slightly diminished when the infarcts are clinically severe than when they are mild. In this connection, it

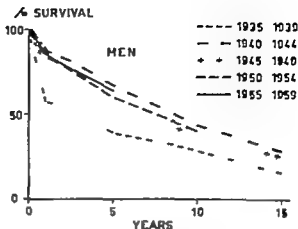
will be remembered that the chances of short term survival diminished greatly with the severity of the infarct.

#### Calendar Year of Infarct

This section on the long term survival after hospitalization will be concluded with a study of how much the survival rate varied with the calendar year of the infarct. Figures 43 and 44 show the survival curves for the men and the women from different five year periods. No curve is given for the women from 1935 through 1939 as there were too few women from those years. The curves were adjusted for age, eliminating the differences between different periods in age at infarction.

The men from the first five years had a highly significantly worse long term outcome than the men from the other periods. What is more surprising the men from 1940 through 1944 showed the best long term outcome while the women from the same five years showed a significantly worse long term outcome than the women

Fig. 43. Percentage survival at different times after infarction among 1,040 men alive four weeks after first infarct grouped by five year periods. Curves adjusted for age.

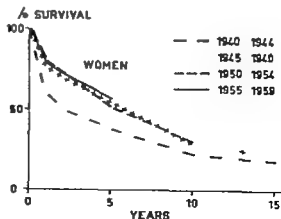


from other years. Here again there was a puzzling difference between the five year period covering the second world war and the other five year periods. As shown in chapter 6 the four week mortality was unexpectedly high among the men during these years, but not among the women. It seems therefore, as if the men getting infarcts during these years had a comparatively better chance of survival in the long run and a proportionately worse chance of survival the first four weeks, while the reverse was true for

the women getting infarcts during these years. As mentioned in chapter 6 however it is not impossible that the discrepancy was caused by differences in hospital facilities during these years.

The curves for the patients from the second half of the 1940's are much like those for the patients from the 1950's. As most of the cases come from these years, the conclusion seems to be justified that the calendar year of the infarct had little to do with the chances of long term survival.

Fig. 44. Percentage survival at different times after infarction among 545 women alive four weeks after first infarct, grouped by five year periods. Curves adjusted for age.



## LONG TERM FUNCTIONAL RECOVERY

Several authors have studied the amount of functional recovery and ability to return to work after myocardial infarction (e.g. Maister et al. 1954, Hsalo et al., 1958, Weiss and Weiss, 1958, Malmcrona et al., 1962 and Blörck and Wedelln, to be published). Blörck et al. (1957) studied the amount of rehabilitation in 85 patients surviving an infarct in their 60's who were hospitalized in Malmö from 1951 through 1953 and who are therefore included in the present series. The trend seems to be toward a more and more optimistic prognosis, especially as regards ability to work after infarction. Once again, however it is hard to compare series from different authors. The series vary in composition and in length of time between infarction and follow up.

The present series was studied for an answer to the following question.

How much angina pectoris did the patients have after their infarct?

How often did they have decreased functional capacity and decompensation after their infarct?

How much did the patients go back to work?

### MATERIAL AND METHODS

The follow up study was done in 1962. At that time 670 of the 2,477 patients with first infarcts were still alive. From these 670 a sample of 200 or 29.9 per cent was drawn representative of the 670 in sex, age and class of infarct. Only one exception

was made to this rule. As there were fewer severe and mild infarcts than there were moderately severe ones, the number of severe and mild infarcts in the sample was raised beyond their rightful proportion to the nearest even number and the number of moderately severe infarcts in the sample reduced accordingly. This could hardly have introduced any source of error worthy of mention. In all other respects the sample was drawn at random.

As seen from table 45 I re-examined 174 or 87 per cent of the 200 at the hospital. Another 8 who refused to come to the hospital for various reasons I examined in their homes. Thus I examined 182 or 91 per cent of the sample personally. In 9 more cases I succeeded in getting a satisfactory amount of information by letter or by telephone. In another case, the records at the hospital had been kept up to date about the patient's state after he left hospital. Thus I got a satisfactory amount of information in 10 others besides the 182 I examined personally making a total of 192, or 96 per cent of the original sample.

Six patients (3 per cent) refused to cooperate in the follow up. It was known that they were still alive however and that they had not been readmitted or seen in the outpatient service of the Department after their infarct. Two women could not be found. I was known to have left the country for some unknown place but nothing could be learned about the other and

Table 45 Follow-up Series of 200 Cases by Sex and Information Available on Their State in 1962

|  | Men        | Women     | Total      | % of 200     |
|--|------------|-----------|------------|--------------|
| <i>Examined in 1962</i>                          |            |           |            |              |
| Medical Department                               |            |           |            |              |
| At Cardiological Laboratory                      | 131        | 43        | 174        | 87.0         |
| At home  | 4          | 4         | 8          | 4.0          |
|  | 135        | 47        | 182        | 91.0         |
| <i>Obtained satisfactory data by other means</i> |            |           |            |              |
| By letter  | 4          | 1         | 5          | 2.5          |
| By telephone                                     | 2          | 2         | 4          | 2.0          |
| From hospital record                             | 1          | —         | 1          | 0.5          |
|  | 7          | 3         | 10         | 5.0          |
| <i>Not examined</i>                              |            |           |            |              |
| Refused to cooperate                             | 3          | 3         | 6          | 3.0          |
| Lost to follow up                                | —          | 2         | 2          | 1.0          |
|  | 3          | 5         | 8          | 4.0          |
| <b>Total</b>                                     | <b>145</b> | <b>55</b> | <b>200</b> | <b>100.0</b> |

It may be that she had been given the wrong name or birthdate in the records.

Table 46 shows the 192 cases by sex, age at infarction and class of infarct. Compared with the total series (table 19 and fig. 16) the patients in the sample were younger when they got their infarct and more often had mild infarcts. The sample comes from the patients who were still alive in 1962, however. It is only natural that it differs from all the cases of first infarcts in these respects, as the short term and long term survival is directly related to the age at infarction and class of infarct.

I divided the angina pectoris into three grades as severe when it was provoked by even mild physical or mental strain, the patients being generally incapable of any kind of work

as moderately severe, when it was provoked by ordinary everyday forms of exertion as slight, when it was only provoked by an extraordinary amount of strain.

I classified the functional capacity according to the criteria of the New York Heart Association (1955).

I evaluated the amount of decompensation from the amount of peripheral edema and the degree of exertional dyspnea. When the edema only involved the instep and ankle I called it mild, and when it covered a larger area I called it severe. When the patients got short of breath on mild exertion, such as walking up one flight of stairs or less, I considered them to suffer from severe dyspnea when dyspnea was only provoked by moderately severe or severe exertion, I called it mild. Whenever I could ob-



Table 46. *Follow-up Series. Distribution into Different Classes of Infarct by Sex and Age at Infarction*

| Sex and Age<br>at Infarct | Severe | Moderately<br>Severe | Class of Infarct |                           |                     | Total |
|---------------------------|--------|----------------------|------------------|---------------------------|---------------------|-------|
|                           |        |                      | Mild             | Normal or<br>Atypical ECG | Unclassi-<br>fiable |       |
| Men                       |        |                      |                  |                           |                     |       |
| 30-49                     | 4      | 20                   | 4                | —                         | 5                   | 33    |
| 50-59                     | 7      | 27                   | 12               | 4                         | —                   | 50    |
| 60-69                     | 4      | 25                   | 5                | 2                         | 5                   | 41    |
| 70 and on                 | 2      | 18                   | 1                | 1                         | 1                   | 18    |
| Total                     | 17     | 83                   | 22               | 7                         | 11                  | 142   |
| Women                     |        |                      |                  |                           |                     |       |
| 30-49                     | —      | 5                    | 1                | —                         | —                   | 6     |
| 50-59                     | 1      | 9                    | 3                | 3                         | 1                   | 17    |
| 60-69                     | —      | 11                   | 2                | 1                         | —                   | 14    |
| 70 and on                 | 3      | 5                    | 1                | 3                         | 1                   | 18    |
| Total                     | 4      | 30                   | 7                | 7                         | 2                   | 50    |
| Both Sexes                |        |                      |                  |                           |                     |       |
| 30-49                     | 4      | 25                   | 5                | —                         | 5                   | 39    |
| 50-59                     | 8      | 36                   | 15               | 7                         | 1                   | 67    |
| 60-69                     | 4      | 36                   | 7                | 3                         | 5                   | 55    |
| 70 and on                 | 5      | 18                   | 2                | 4                         | 2                   | 31    |
| Grand Total               | 21     | 115                  | 29               | 14                        | 13                  | 192   |

tain reliable information on one or more of these points for the 10 patients whom I did not examine personally I included them in the analysis on the point or points in question.

The data on the patients' angina pectoris, functional capacity and car-

diac decompensation serving as background for the following analyses apply to the month before the patients were re-examined. The data for return to work apply to the time directly following their sickness absence for the infarction.

Table 47. *Follow-up Series. Mean Number of Years Since Infarct in the 192 Cases, by Sex and Class of Infarct*

| Class of Infarct      | Mean No. of Years Since Infarct |           |            |
|-----------------------|---------------------------------|-----------|------------|
|                       | Men                             | Women     | Both Sexes |
| Severe                | 5.24 (17)                       | 4.53 (4)  | 5.15 (21)  |
| Moderately severe     | 6.78 (85)                       | 6.77 (30) | 6.78 (115) |
| Mild                  | 7.23 (22)                       | 10.56 (7) | 8.04 (29)  |
| Normal or typical ECG | 9.14 (7)                        | 9.59 (7)  | 9.36 (14)  |
| Total                 | 6.79 (131)                      | 7.60 (48) | 7.01 (179) |
| Unclassifiable        | 8.01 (11)                       | 6.03 (7)  | 7.70 (18)  |
| Grand Total           | 6.89 (142)                      | 7.54 (55) | 7.26 (197) |

Figures in brackets denote number of patients in group

Table 47 gives the mean number of years between the infarct and follow up in different age and sex groups. To express the length of the interval between infarction and follow up in another way in 75 per cent of the sample the interval between the myocardial infarct and follow up ranged between 2 and 11 years, in 19 per cent it ranged between 8 and 10 years and in 6 per cent it amounted to 11 years or more. In no instance was it less than 2 years.

## RESULTS AND ANALYSIS

### *Frequency of Angina Pectoris*

Figure 45 shows the percentages of patients over and under 60 at the time of infarction, grouped first according to whether or not they had angina before their infarct, and then according to whether they had severe, moderately severe, slight and no angina at the time of follow up. Table 48 shows the same percentages in the

cases divided by sex. The sexes do not differ significantly in any group.

Altogether 101 in the sample or 52.0 per cent, had no angina pectoris before their infarct, as against 50.8 per cent of all the patients with first infarcts (chap 2). The patients who had angina before their infarct were more apt than the others to have it at the time of follow up and to have it more severely. The patients of 60 and over at the time of infarction were less apt to have angina later on than the younger patients, and more apt to have it in milder form. The men under 60 at the time of infarction had angina statistically significantly more often in the subsequent course than the men who got their infarct when they were older. It is not clear why. It may be that the decrease in activity with aging is apt to keep the angina from being manifested. It may also be that the pain threshold is raised with age. Finally it may be that the longer average duration of the angina

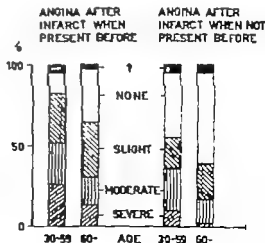


Fig. 45 Percentage distribution of 91 patients with and 101 patients without angina pectoris before their infarcts by age and amount of angina at follow up.

Table 46. *Follow-up Series. Distribution into Different Classes of Infarct by Sex and Age at Infarction*

| Sex and Age<br>at Infarct | Severe | Moderately<br>Severe | Class of Infarct |                           |                     | Total |
|---------------------------|--------|----------------------|------------------|---------------------------|---------------------|-------|
|                           |        |                      | Mild             | Normal or<br>Atypical ECG | Unclassi-<br>fiable |       |
| Men                       |        |                      |                  |                           |                     |       |
| 30-49                     | 4      | 20                   | 4                | —                         | 5                   | 33    |
| 50-59                     | 7      | 27                   | 13               | 4                         | —                   | 50    |
| 60-69                     | 4      | 25                   | 5                | 2                         | 5                   | 41    |
| 70 and on                 | 2      | 13                   | 1                | 1                         | 1                   | 18    |
| Total                     | 17     | 85                   | 23               | 7                         | 11                  | 142   |
| Women                     |        |                      |                  |                           |                     |       |
| 30-49                     | —      | 8                    | 1                | —                         | —                   | 8     |
| 50-59                     | 1      | 9                    | 3                | 3                         | 1                   | 17    |
| 60-69                     | —      | 11                   | 2                | 1                         | —                   | 14    |
| 70 and on                 | 3      | 5                    | 1                | 3                         | 1                   | 13    |
| Total                     | 4      | 33                   | 7                | 7                         | 2                   | 53    |
| Both Sexes                |        |                      |                  |                           |                     |       |
| 30-49                     | 4      | 28                   | 5                | —                         | 5                   | 39    |
| 50-59                     | 8      | 36                   | 16               | 7                         | 1                   | 67    |
| 60-69                     | 4      | 36                   | 7                | 3                         | 5                   | 55    |
| 70 and on                 | 5      | 18                   | 2                | 4                         | 2                   | 31    |
| Grand Total               | 21     | 115                  | 29               | 14                        | 13                  | 192   |

tain reliable information on one or more of these points for the 10 patients whom I did not examine personally I included them in the analysis on the point or points in question.

The data on the patients' angina pectoris, functional capacity and car-

diac decompensation serving as background for the following analyses apply to the month before the patients were re-examined. The data for return to work apply to the time directly following their sickness absence for the infarction.

Table 47. *Follow-up Series. Mean Number of Years Since Infarct in the 192 Cases, by Sex and Class of Infarct*

| Class of Infarct      | Mean No. of Years Since Infarct |                  |                   |
|-----------------------|---------------------------------|------------------|-------------------|
|                       | Men                             | Women            | Both Sexes        |
| Severe                | 5.24 (17)                       | 4.53 (4)         | 5.15 (21)         |
| Moderately severe     | 6.78 (85)                       | 6.77 (30)        | 6.78 (115)        |
| Mild                  | 7.23 (23)                       | 10.56 (7)        | 8.04 (29)         |
| Normal or typical ECG | 9.14 (7)                        | 9.59 (7)         | 9.36 (14)         |
| <b>Total</b>          | <b>6.79 (131)</b>               | <b>7.60 (48)</b> | <b>7.01 (179)</b> |
| Unclassifiable        | 8.01 (11)                       | 6.03 (2)         | 7.70 (13)         |
| <b>Grand Total</b>    | <b>6.89 (142)</b>               | <b>7.54 (50)</b> | <b>7.06 (192)</b> |

Figures in brackets denote number of patients in group.

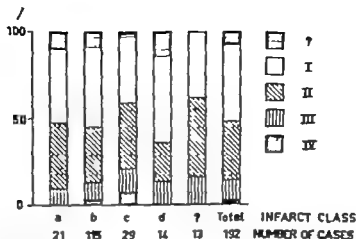


Fig. 47 Percentage distribution of 192 patients in different classes of infarct and functional groups at follow-up (defined by New York Heart Association, 1955) — severe infarct b = moderately severe infarct — mild infarct d = normal or atypical ECG ? = unclassifiable

figure shows little difference between the patients below and above 60. The reason for the larger percentage of unclassifiable cases in the older group is that they included more patients who were so disabled by other diseases that it was hard to judge how well their hearts performed.

Altogether 44.3 per cent of the patients belonged to functional group I who were not at all restricted physically and 33.0 per cent to group II who were only slightly restricted; thus 78.2 per cent of both age groups were not at all or only slightly restricted in physical capacity.

Figure 47 shows the functional capacity in the cases divided according to the class of infarct. There were only a few patients with severe, mild and unclassifiable infarcts and no statistically significant differences are

forthcoming. Nor is any distinct trend visible.

#### Cardiac Decompensation

Table 49 shows the patients getting their infarcts before and after 60 divided by the amount of decompensation at follow-up, i.e., the amount of edema and exertional dyspnea. Here again there was little difference between the two age groups. Nor was there any difference between the sexes.

Malmcrona et al. (1962) found decompensation in 43 per cent of patients getting infarcts before they were 50. In the present sample, 45 per cent of the patients getting their infarcts before they were 60 had dyspnea at follow-up and 10 per cent edema. Hjalte et al. (1958) found decompensation in 41 per cent of their

Table 49 *Follow-up Series Percentage Distribution of Different Degrees of Decompensation in the 192 Patients at Follow-up by Age at Infarction*

| Age   | No. of Cases | Edema |      |        |                     |
|-------|--------------|-------|------|--------|---------------------|
|       |              | None  | Mild | Severe | Information Lacking |
| 30—59 | 106          | 86.8  | 8.5  | 1.9    | 2.8                 |
| 60 on | 86           | 80.2  | 9.3  | 5.8    | 4.7                 |
| Total | 192          | 83.9  | 8.9  | 3.6    | 3.6                 |

| Age   | No. of Cases | None | Dyspnea                        |                    | Information Lacking |
|-------|--------------|------|--------------------------------|--------------------|---------------------|
|       |              |      | On Moderate or Severe Exertion | On Slight Exertion |                     |
| 30—59 | 106          | 51.9 | 36.8                           | 8.5                | 2.8                 |
| 60 on | 86           | 55.8 | 29.1                           | 11.6               | 3.5                 |
| Total | 192          | 53.  | 33.3                           | 9.9                | 3.1                 |

cases. Thus the series agree well on this point.

It is surprising that there was so little difference between the patients above and below 60 in this series. There are no figures in the literature with which these can be compared. In all likelihood, however the frequency and amount of cardiac decompensation increases with aging if this is so, the observations in the present series indicate that patients getting their infarcts when they are young are more apt to suffer from cardiac decompensation after their infarct than people who get their infarcts when they are older.

### Working Capacity

Only 95 patients, or 49.5 per cent of the sample, were able to state with any certainty how long they had been declared medically unfit or partially unfit for work after they were discharged from hospital. As seen from table 50 the average length of certified inability decreased with the age of the patient at the infarct. One reason for this is probably that the young patients usually had heavier or more active kinds of work, and the physicians writing the certificates probably felt that it would take longer for them to be able to resume work than if they had had lighter work.

Table 50 *Follow-up Series Length of Medically Certified Inability for Work After Infarct in the 192 Cases by Age at Infarction*

| Age   | Length of<br>Certified Working<br>Inability Known | Months of<br>Average | Certified Inability<br>Range | Length of<br>Certified Working<br>Inability Unknown |
|-------|---|----------------------|------------------------------|---|
| 30—59 | 33  | 6.0                  | 1—18                         | 8   |
| 50—59 | 47  | 5.2                  | 1—24                         | 11  |
| 60—69 | 20  | 4.8                  | 1—10                         | 36  |
| 70 on | 1   | (1.0)                | —                            | 29  |
| Total | 95  |                      |                              | 57  |

Fig. 48. Amount of work men did after first infarcts.

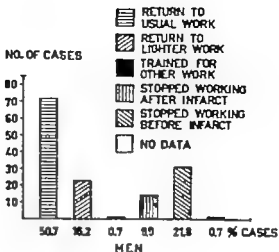


Figure 48 shows the amount of work the men did after their infarct. Some of the patients listed under "Return to Usual Work" changed to another job, but the work they did there was equivalent to what they had done before. "Return to Lighter Work" includes the men who changed to less tiring work physically, e.g. from being a shipworker to a caretaker at the shipyard, or from manual work in a storeroom to officework in the storeroom. Only 1 patient was trained for another kind of work. Fourteen did not return to work. Thirty-one said that they had already stopped working before their infarct, mostly because they had reached the age of retirement.

Figure 49 shows the corresponding figures for the women. This figure does not give as much information as the foregoing. Not less than 44 per cent of the women who said they had not worked either before or after their infarct kept house for their families,

and though they were not gainfully employed, many of them worked extremely hard. Furthermore, when the women said that they worked they generally meant that they did part time work away from home.

Table 51 shows the amount of work the men did after their infarct in re-

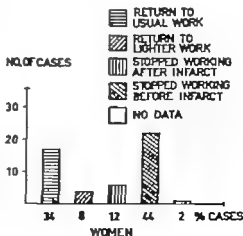


Fig. 49. Amount of work women did after first infarcts.

Table 51 *Follow-up Series Amount of Work Done by the 142 Men After Their Infarct by Age at Infarct*

| Age   | Return to<br>Old Work | Return to<br>Lighter Work | Trained for<br>Other Work | Stopped<br>Work After<br>Infarct | Stopped<br>Work<br>Before<br>Infarct | Information<br>Lacking | Total |
|-------|-----------------------|---------------------------|---------------------------|----------------------------------|--------------------------------------|------------------------|-------|
| 30-40 | 24                    | 9                         | —                         | —                                | —                                    | —                      | 33    |
| 50-59 | 29                    | 12                        | —                         | 6                                | 3                                    | —                      | 50    |
| 60-69 | 16                    | 3                         | 1                         | 7                                | 14                                   | 1                      | 41    |
| 70 on | 3                     | —                         | —                         | 1                                | 14                                   | —                      | 18    |
| Total | 72                    | 23                        | 1                         | 14                               | 31                                   | 1                      | 142   |

lation to their age when they got the infarct. All the men under 50 went back to work, either to their old work or to lighter work. The same was true of 82 per cent of the men in their 50's of 44 per cent in their 60's and of 17 per cent in their 70's the differences between the ages in this respect were even greater than would appear from these percentages, for most of the 70 year olds and some of the 60 year olds were only doing part time work before their infarct. The amount of work the men did after their infarct was not related to the class of the infarct one would have expected a relationship here, in view of the worse figures for survival after the severe infarct.

It is hard to draw any conclusions from the figures for the women. They show the same trend with age as the men, however.

Master et al (1954) reported that 69.7 per cent of their 343 patients returned to full or part time work 67 per cent of the men in the present sample did so which is almost the same percentage. Malmcrona et al. (1962) re-examined 150 patients who got their infarct before they were 55

and who had previously worked full time at follow up 3 years and 5 months after the infarct, on the average, 69 per cent of the patients were still fully capable of working 18 per cent were not as capable as before and 13 per cent could not do any work. The corresponding figures for the present sample are about the same thus 66 per cent of the 80 men between 30 and 59 who worked full time before their infarct went back to the same work they had done before, 26 per cent went back to lighter work, and 8 per cent stopped working. The earlier Malmö study by Björck et al. (1957) and a similar investigation in Stockholm (Björck and Wedelin, to be published) gave essentially the same results as the ones obtained in the present analysis this is seen in table 52.

The observation that the patients were less apt to go back to work the older they were when they got their infarct is not in keeping with the observations that age had little effect on functional capacity and that the young patients were more prone to angina pectoris after their infarct than were the old ones. The reason for this dis

**Table 52 Patients in Three Swedish Series Who Worked Full Time Before Their Infarct Distributed by Whether They Did Same Work, Lighter Work or No Work Afterwards Both Sexes**

|  | No. Fully<br>Occupied<br>Before Infarct | Returned to<br>Old Work<br>No. | Returned to<br>Lighter Work<br>No. | Stopped<br>Working<br>No. |
|--|---|--------------------------------|------------------------------------|---------------------------|
| Malmö, (Björck and<br>Trulsson, 1957)                  | 42                                      | 20 (63)                        | 8 (19)                             | 5 (12)                    |
| Stockholm, (Björck<br>and Wedelin,<br>to be published) | 120                                     | 67 (56)                        | 32 (27)                            | 21 (17)                   |
| Malmö, present series                                  | 136                                     | 89 (65)                        | 37 (26)                            | 20 (15)                   |

crepancy is probably that the old patients did not have the same incentive to go back to work as the young patients. It seems reasonable to conclude therefore that even though young pa-

tients are more apt to go back to their old work after their infarcts than old patients, they have a worse functional long term outcome in comparison with others their age.



logy in Malmö for the number of healed infarcts noted, concluded that healed infarcts were not always noted because of the way the dissecting was done or the records were written. It may be assumed, however, that the figures from the present cases in which the patients died from fresh infarcts, give more reliable figures for earlier infarction than do the records of patients dying from other causes as well.

It is not certain how these antagonistic sources of error affected the results in the present study. Lee et al. (1957) found that 25 per cent of the earlier infarcts found on the autopsy of 500 persons dying from acute infarction had not been detected during life. On the whole, however, the reports in the literature on the frequency of undetected infarction vary a great deal. The present analysis would indicate that infarction is often overlooked during life, but how often is impossible to conclude from the material on hand.

The rise in the frequency of healed infarcts with age seen in figure 50 is what one would expect and is in keeping with the reverse correlation between age and pain at infarction demonstrated in chapter 3. The patients between 30 and 49 showed an unexpectedly high frequency. It may be, however, that the pathologist examines the myocardium more closely than he would otherwise in a case of infarction at an unusually young age and is more apt to find healed infarcts than he would otherwise. How much this affects the figures, impossible to say.

If it has no effect this would be still another way in which the young patients differ from the older ones.

It is not clear what caused the significant sex difference. The present series contained far more young men than young women, however. Coronary heart disease is much less common among young women than young men, and it may follow from this that men have generally had coronary lesions longer when they get myocardial infarcts than do women when they get infarcts. This may explain the difference between the sexes observed here.

The calendar variation shown in figure 51 is not greater than could have been due to coincidence in either sex. The last three five year periods, which contained most of the cases, showed a steady decrease, however. Thus it may be that there really was a drop from year to year though so small that the present material was not large enough to provide it with statistical significance.

#### FREQUENCY OF CARDIAC RUPTURE

Cardiac rupture with hemopericardium and cardiac tamponade was observed in 104 or 12.8 per cent of the 811 autopsies performed in the cases of first infarct from 1935 through 1959. Table 54 shows the ruptures by age and sex of the patients. As seen there the frequency of rupture rose with age, and there were more among the women than the men, regardless of age. The total frequency of rupture among the men after their

Table 54 Number and Percentage Distribution of Cardiac Rupture Among the 811 Patients from Table 53 by Sex and Age at Infarction

| Age   | Men              |                | Women            |                | Total            |                |
|-------|------------------|----------------|------------------|----------------|------------------|----------------|
|       | No. of Autopsies | Ruptures No. % | No. of Autopsies | Ruptures No. % | No. of Autopsies | Ruptures No. % |
| 30-39 | 0                | — —            | —                | — —            | 0                | — —            |
| 40-49 | 19               | 1 (5.3)        | —                | — —            | 21               | 1 (4.8)        |
| 50-59 | 100              | 9 9.0          | 21               | 3 (14.3)       | 121              | 12 9.9         |
| 60-69 | 13               | 17 9.7         | 109              | 1 13.8         | 281              | 32 11.4        |
| 70-79 | 12               | 19 15.8        | 144              | 34 23.6        | 256              | 43 16.8        |
| 80 on | 34               | 11 32.4        | 36               | 18 50.0        | 71               | 16 22.6        |
| Total | 403              | 52 12.9        | 318              | 52 16.4        | 811              | 104 12.8       |

Table 55 Number and Percentage Distribution of Cardiac Rupture Among All 2477 Cases of First Infarct from 1935 Through 1959 by Sex and Age at Infarction

| Age   | Men             |                | Women           |                | Total           |                |
|-------|-----------------|----------------|-----------------|----------------|-----------------|----------------|
|       | No. of Patients | Ruptures No. % | No. of Patients | Ruptures No. % | No. of Patients | Ruptures No. % |
| —39   | 31              | — —            | 5               | — —            | 36              | — —            |
| 40-49 | 183             | 1 0.5          | 33              | — —            | 216             | 1 0.5          |
| 50-59 | 436             | 9 2.0          | 131             | 3 2.3          | 567             | 12 2.1         |
| 60-69 | 344             | 1 3.1          | 318             | 13 4.1         | 662             | 22 3.3         |
| 70-79 | 321             | 19 5.9         | 370             | 31 8.4         | 691             | 43 6.2         |
| 80 on | 70              | 8 11.4         | 64              | 10 15.6        | 134             | 18 13.4        |
| Total | 1,801           | 32 1.8         | 890             | 52 5.9         | 2,691           | 84 3.1         |

age distribution was adjusted to that of the women, amounted to 11.5 per cent, which is probably significantly less than the women's 16.4 per cent. In table 55 the 104 ruptures are projected against all the first infarcts in the series. This table gives the same picture as table 54, a rise in the frequency of rupture with age and a higher frequency among the women than among the men at every age.

The variation in the frequency of cardiac rupture from five year period to five year period is seen from table 56. The variation is no greater than could have been due to chance. Nor is any distinct trend visible. Thus there was no change in the frequency of rupture during the course of the 25 years under study.

Altogether 68.6 per cent of the patients dying within the first four weeks died within one week of the first clinical evidence of infarction. 73.0 per cent of the patients with rupture did so. The days after the infarct that the deaths within a week took place are seen from figure 52. As seen, most of the ruptures took place within the first 24 hours.

Several authors have attempted to

Table 56 Percentage of Ruptures in All 2477 Cases of First Infarcts from 1935 Through 1959 by Five Year Period

| Five Year Period | % Ruptures in All Cases |
|------------------|-------------------------|
| 1935-1939        | 4.3                     |
| 1940-1944        | 3.8                     |
| 1945-1949        | 4.1                     |
| 1950-1954        | 3.1                     |
| 1955-1959        | 3.7                     |

obvious from Ekvall's (1955) analysis of the relationship between the time of hospitalization and the short term mortality. Ekvall found that 67 out of 212 patients hospitalized within four weeks, or 32 per cent, died within four weeks of admission. This rate is like that in the Malmö series: one would not have expected this, for only 29 per cent of Ekvall's patients were admitted within 24 hours, 43 per cent within 48 hours and 5 per cent within 3 days, as against 69, 70 and 74 per cent within the same periods in the present series.

To sum up: it was impossible to determine how many patients with myocardial infarction were missing from the series. Because of the conditions in Malmö the present series is probably more representative of the cases of myocardial infarction diagnosed in routine medical practice in Malmö than most hospital series are of their underlying populations.

#### MYOCARDIAL INFARCTION IN OLD PATIENTS

Table 4 giving the ratios between men and women at different ages in the present series, shows that the men greatly outnumbered the women among the young patients, but as the patients grew older the preponderance of men became smaller and after the age of 70 there was one woman to every man. This does not mean that old women are as liable to myocardial infarction as are old men. There are more old women in the general population than there are old men, and figure 28 indicates that, compared with

the number of same-sexed, same-aged persons in the underlying population, old men continue to be more liable to infarction than do old women. It is important to recognize this, for it is often stated that when women grow older they become just as prone as men to atherosclerosis and its different manifestations. Plotz (1957) for example, said after going through the literature on the sex ratio in coronary disease that in old age the two sexes were equally vulnerable.

It is still a matter of hypothesis why men are more prone than women to myocardial infarction and coronary heart disease. Dock (1963) has recently published a survey of the theories and a list of the latest references.

Several authors state that myocardial infarction is most apt to occur between the ages of 50 and 69 and after that less frequently. Doscher and Poindexter (1950) and Wright et al. (1954) found that persons in their 50's were most vulnerable, while Minix and Katz (1947) found that persons in their 60's were most vulnerable, as did also Eckerström (1951) and Ekvall (1955). Judging at first sight from the present series the men were most liable to infarction in their 60's and the women in their 70's. After the figures were projected against the underlying population however the men also proved to be most liable in their 70's.

Thus the same was noted in the Malmö series as by others (e.g. Peel 1955) that the liability to infarction rose with advancing age up to a cer-

tain time of life and then fell. Here the peak frequency was noted in the 70's others have reported other ages to be most vulnerable. This observation of a drop in frequency of myocardial infarctions in old people is puzzling for international statistics show a rise in the frequency of death from coronary heart disease with aging right up to the end (Schettler 1961). It may be that the drop in the rate of myocardial infarction in elderly people so many have observed does not reflect the true circumstances. In the first place many old patients die soon after the infarction starts. Thus probably more of them die before they reach hospital than do younger patients. Secondly there is a small rise in the rate of painless infarction with advancing age. As private practitioners without an electrocardiograph often have no other symptoms than pain to go by, they are probably more apt to miss the diagnosis when the patients are old. Thirdly, it is also possible that some extremely old patients are not sent to hospital even if the physician suspects or knows they have a myocardial infarct. It is not impossible, therefore, that the drop in the rate of hospitalized patients among the old does not reflect the true frequency of myocardial infarction among them.

#### MYOCARDIAL INFARCTION IN YOUNG PATIENTS

To go to the other end of the age scale, the youngest patients in the series differed surprisingly from the others in several respects. While the four week

mortality rate was closely related to the age at infarction from the age of 40 on (fig. 30) the patients under 40 had a rate of 70.7 per cent which was higher than that of the 50 year olds. Secondly the patients under 40 had a relatively poor long term outcome. Thirdly they had antecedent angina pectoris just as often as the older patients, though usually not for as long a time. Fourthly they seemed to show a large number of old, healed infarcts on autopsy. Many of them also had antecedent hypertension, but this was to be expected from reports in the literature.

Because of this I shall analyze these young patients a little more closely. The series contained 38 cases of a first infarct in patients under 40, including 33 men and 5 women.

One of the women had had diabetes for 20 years when she got her infarct at the age of 38. Another aged 34 had chronic nephritis with hypertension. If it is true as supposed, that diabetes, hypertension and obesity as well as hypercholesterolemia and hereditary loading predispose a person to coronary heart disease, there were predisposing factors in these two cases. A third woman aged 33 had combined mitral stenosis and insufficiency as the result of rheumatic fever. The infarct in her case was assumed to be due to an embolus. The patient died three years later from decompensation, but unfortunately permission for autopsy was denied. A fourth, aged 39 had been excessively obese and had gone down 42 Kg. by dieting and taking thyroid compounds during a

logy in Malmö for the number of healed infarcts noted, concluded that healed infarcts were not always noted because of the way the dissecting was done or the records were written. It may be assumed, however that the figures from the present cases, in which the patients died from fresh infarcts, give more reliable figures for earlier infarction than do the records of patients dying from other causes as well.

It is not certain how these antagonistic sources of error affected the results in the present study. Lee et al (1957) found that 25 per cent of the earlier infarcts found on the autopsy of 500 persons dying from acute infarction had not been detected during life. On the whole, however the reports in the literature on the frequency of undetected infarction vary a great deal. The present analysis would indicate that infarction is often overlooked during life but how often is impossible to conclude from the material on hand.

The rise in the frequency of healed infarcts with age seen in figure 50 is what one would expect and is in keeping with the reverse correlation between age and pain at infarction demonstrated in chapter 3. The patients between 30 and 49 showed an unexpectedly high frequency. It may be however that the pathologist examines the myocardium more closely than he would otherwise in a case of infarction at an unusually young age and is more apt to find healed infarcts than he would otherwise. How much this affects the figures is impossible to say.

If it has no effect this would be still another way in which the young patients differ from the older ones.

It is not clear what caused the significant sex difference. The present series contained far more young men than young women, however. Coronary heart disease is much less common among young women than young men, and it may follow from this that men have generally had coronary lesions longer when they get myocardial infarcts than do women when they get infarcts. This may explain the difference between the sexes observed here.

The calendar variation shown in figure 51 is not greater than could have been due to coincidence in either sex. The last three five year periods, which contained most of the cases, showed a steady decrease, however. Thus it may be that there really was a drop from year to year though so small that the present material was not large enough to provide it with statistical significance.

#### FREQUENCY OF CARDIAC RUPTURE

Cardiac rupture with hemopericardium and cardiac tamponade was observed in 104 or 17.8 per cent of the 811 autopsies performed in the cases of first infarct from 1935 through 1959. Table 54 shows the ruptures by age and sex of the patients. As seen there the frequency of rupture rose with age and there were more among the women than the men, regardless of age. The total frequency of rupture among the men, after their

## REINFARCTS

### PRESENT MATERIAL

As seen from table 1 the total series contained 42 cases of a reinfarct. In 103 of these 42 there were not enough or not reliable data for the analyses I wanted to make. In 38 cases, the first infarct had been diagnosed and treated by a private practitioner in the home. In 71 cases it had been treated at a hospital outside Malmö or at our Department before 1935. In 44 cases the diagnosis was made later by the physician writing the patient's history for the files of the Medical Department, occasionally only on the basis of the past history but most often on the grounds of objective electrocardiographic evidence of past myocardial infarction.

This left 74 pure cases of reinfarction in which the first infarct was treated at the Medical Department from 1935 on (and were thus included in the first infarcts in the series). When comparing the observations in these 74 cases with those in the cases clinically judged to be ones of a first infarct, it must be borne in mind that some of the latter cases are really ones of reinfarction, the first infarcts having been symptomless or so atypical

that the diagnosis was not made (chap. 8). Thus any differences between the cases of first and recurrent infarcts might have been still larger if more of the past infarcts had been discovered.

### CHARACTERISTICS OF REINFARCT CASES

#### *Age and Sex Distribution*

The 324 reinfarcts consist of 782 second infarcts, 39 third infarcts and 3 fourth infarcts. The age and sex distribution of the patients with a second and third infarct are given in table II together with the four week mortality. The age distribution is seen again in figure 53: there separate curves are plotted for the men with second and third infarcts, but the women have only one curve, i.e., for second infarcts, as only 10 of them had third infarcts. For the sake of comparison this figure also contains bars showing the age distribution of all the four week survivors of a first infarct. The men with reinfarcts are distributed about the same by age as the men who survived their first infarcts, but the women with reinfarcts tend to be of

Table 57 The 282 Case of a Second Infarct and 39 of a Third Infarct from 1935 Through 1959 by Sex Four Week Mortality and Age at Infarction

| Age            | Men |                        | Women |                        | Both Sexes |                        |
|----------------|-----|------------------------|-------|------------------------|------------|------------------------|
|                | No. | No. Dead Within 4 Week | No.   | No. Dead Within 4 Week | No.        | No. Dead Within 4 Week |
| Second Infarct |     |                        |       |                        |            |                        |
| 30-39          | 2   | —                      | 1     | —                      | 3          | 1                      |
| 40-49          | 25  | 6                      | 2     | —                      | 27         | 8                      |
| 50-59          | 66  | 20                     | 10    | 4                      | 76         | 24                     |
| 60-69          | 61  | 23                     | 4     | 70                     | 106        | 45                     |
| 70-79          | 26  | 15                     | 33    | 15                     | 59         | 30                     |
| 80-89          | 6   | 5                      | 5     | 4                      | 11         | 9                      |
| Total          | 180 | 1                      | 96    | 46                     | 282        | 117                    |
| Third Infarct  |     |                        |       |                        |            |                        |
| 30-39          | 1   | 1                      | —     | —                      | 1          | 1                      |
| 40-49          | 4   | 1                      | —     | —                      | 4          | 1                      |
| 50-59          | 11  | 4                      | —     | —                      | 11         | 4                      |
| 60-69          | 10  | 1                      | 5     | 2                      | 15         | 3                      |
| 70-79          | 3   | 1                      | 3     | 2                      | 8          | 3                      |
| 80-89          | —   | —                      | —     | —                      | —          | —                      |
| Total          | 29  | 8                      | 10    | 4                      | 39         | 12                     |

der than the women who survived their first infarcts. This would indicate that old women are more liable to have reinfarcts than young ones while this is not true for the men. This will be demonstrated more convincingly later on.

The ratio of men to women was 1.9:1 for the second infarcts and 2.9:1 for the third infarcts as opposed to 1.8:1 for the first infarcts. These ratios did not differ significantly.

#### Distribution into Infarct Classes

Table 58 shows the percentage distribution of the second infarcts into the different classes of infarct and the four week mortality rate in each class, as well as the corresponding figures for the first infarcts (from table 19). As seen the first and second infarcts contained about the same proportion

of mild, moderately severe and severe infarcts. The second infarcts contained a significantly higher proportion of cases with a normal or atypical electrocardiogram this was probably because it is harder to establish the presence of renewed infarction by electrocardiographic means. On the other hand, they contained a highly significantly lower proportion of unclassified cases. This is harder to explain. The likelihood is however that both the patients and attending physicians were more observant of detail in the case of a second infarct, and this made it easier to classify the infarct.

The second and first infarcts did not differ significantly in the mortality associated with different classes of infarct though the mortality in the two largest classes, the severe and mo-

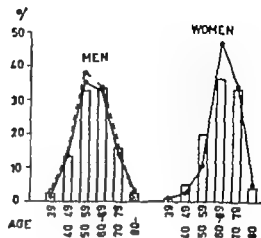


Fig. 53 Age distribution of the men and women with first infarct from 1933 through 1950. Bars = first infarct, lines = second infarct, dotted curve = third infarct.

derately severe infarcts, tended to be higher in the cases of second infarction.

There were too few cases of a third infarct to allow any conclusions of value, but on the whole they showed about the same picture as the second infarcts.

#### Four Week Mortality

The four week mortality in the cases of a second infarct divided by age and sex is seen from table 59; the total

mortality amounted to 41.6 per cent. The mortality for all the men was lower than for all the women. This was mostly due to the women being older when the age distribution of the men was adjusted to that of the women, the mortality rose to 47.0 per cent, which is not far from the women's 47.9 per cent. Thus the same was true here as of the first infarcts, that the short term mortality was the same for both sexes.

The four week mortality for all the

Table 59 The 282 Second and 2477 First Infarcts from 1933 Through 1950 Compared for Percentage Distribution by Age and Sex of Infarct and Four Week Mortality Rate for Each

| Class of Infarct         | Second Infarcts |                       | First Infarcts |                       | % Died Within 4 Weeks |                       |
|--------------------------|-----------------|-----------------------|----------------|-----------------------|-----------------------|-----------------------|
|                          | no. of cases    | % Died Within 4 Weeks | no. of cases   | % Died Within 4 Weeks | % Died Within 4 Weeks | % Died Within 4 Weeks |
| Severe                   |                 |                       | 15             | 15                    | 90.9                  | 63.5                  |
| Moderate                 | 167             | 48                    | 212            | 23.1                  | 28.7                  | 25.7                  |
| Mild                     | 12              | 17                    | 42             | 8.1                   | (0.0)                 | 1.2                   |
| Normal (typical ECG)     | 20              | 10                    | 128            | 7.1                   | 76.1                  | 11.0                  |
| Not detected until 1 day | 2               | 2                     | 87             | 1.8                   |                       | 88.0                  |
| Incalculable             | 10              | 1                     | 38             | 9.8                   | (10.0)                | 27.6                  |
| Total                    | 282             | 117                   | 1000           | 100.0                 | 41.6                  | 31.6                  |



Table 59 The Four Week Mortality Rate in the 263 Cases of a Second Infarct from 1935 Through 1959 by Sex and Age of Infarction

| Age   | Percentage Four Week Mortality |        |        |
|-------|--------------------------------|--------|--------|
|       | Men                            | Women  | Total  |
| 30-39 | —                              | —      | —      |
| 40-49 | (24.0)                         | —      | (20.6) |
| 50-59 | 30.3                           | (40.0) | 31.6   |
| 60-69 | 41.0                           | 41.4   | 41.2   |
| 70-79 | (57.7)                         | 43.5   | 50.8   |
| 80-89 | —                              | —      | (81.8) |
| Total | 28.2                           | 47.9   | 41.6   |

When percentages are lacking, it means that there were less than 10 cases in the group. Percentages in brackets mean that there were only 10-19 cases in the group.

first infarct amounted to 34.0 per cent (31.8 per cent for the men and 37.5 per cent for the women) which is significantly lower than the 41.2 per cent for the second infarct. The difference is not entirely significant for the men ( $0.10 > p > 0.05$ ) but it is probably significant for the women. As seen from figure 23, there was not much difference in the ages of the patients with first and second infarcts, and so this was no explanation for the difference in mortality. Thus, when the age distribution of the first infarct was adjusted to that of the second infarct, the mortality amounted to 29.0 per cent for the men and 33.2 per cent for the women.

In other words, the four week mortality was higher in the cases of a second infarct than in the ones of a first infarct even after differences in age and sex were eliminated. Table 58 shows that the distribution into severe, moderately severe and mild infarcts was about the same in the first

and second infarcts and so the difference in four week mortality could not be explained by differences in class of infarct.

The reports in the literature on this point are not unanimous. Doscher and Poindexter (1930) found that the mortality was higher after a second than a first infarct both in their own series and in a series they collected from the literature. Billings et al (1939) made the same observation. Honey and Truelove (1953) could not find any conclusive difference.

#### RISK OF REINFARCTION

Different authors have used different methods for expressing the risk of recurrence. Some give the rate of previous infarction in a series. Table 60 compares the rate of reinfarction in the present series with that in four other series. The first set of figures for the present series in this table

Table 60 Percentage of Reinfarcts in Present Case from 1935 Through 1959 First Reckoned from All Reinfarct and Then Only from Cases Who a First Infarct Are Included in Series Compared with Percentage Reinfarcts in Other Series

| Present Series                           | Reinfarcts |             |
|--|------------|-------------|
|  | Number     | One or More |
| All reinfarct                            | 83.3       | 11.1        |
| First infarct included in present series | 88.4       | 11.6        |
| Wilder et al (1939)                      | 67.1       | 27.9        |
| Wilder and Katz (1947)                   | 92.2       | 5           |
| Doscher and Poindexter (1930)            | 66.5       | 13.3        |
| Wright et al (1944)                      | 78.0       | 22.1        |

Table 61 Number of Second Infarcts and Number Per Hundred Year of Exposure at Different Intervals After First Infarct in 907 or Week Survivors from 1935 Through 1954 by Sex and Age at Infarct

| Time Since<br>1st Infarct | Under 60 (320 Patients) |                  |  | 60 and over (587 Patients) |                  |  |
|---------------------------|-------------------------|------------------|--|----------------------------|------------------|--|
|                           | Yrs. of<br>Exposure     | No. of<br>Recurs | Recurs per<br>100 Years of<br>Exposure | Yrs. of<br>Exposure        | No. of<br>Recurs | Recurs per<br>100 Years of<br>Exposure |
| 1-5 mos.                  | 123.7                   | 16               | 12.9                                   | 107.0                      | 3                | 4.7                                    |
| 6-12 mos.                 | 130.9                   |                  | 3.8                                    | 107.0                      | 10               | 9.8                                    |
| 1-2 yrs.                  | 401.0                   | 21               |  | 797.0                      | 14               | 4.7                                    |
| 3-4 yrs.                  | 261.0                   |                  | 2                                      | 169.0                      | 2                | 1.2                                    |
| 5-9 yrs.                  | 761.5                   | 11               | 4.2                                    | 127.0                      |                  | 3.9                                    |
| 10-19 yrs.                | 8.0                     | 1                | 1.2                                    | 79.0                       | 1                | 3.4                                    |
| Total                     | 1,271.1                 | 61               | 4.8                                    | 831.5                      | 37               | 4.4                                    |

| Time Since<br>1st Infarct | Under 60 (92 Patients) |                  |  | 60 and over (254 Patients) |                  |  |
|---------------------------|------------------------|------------------|--|----------------------------|------------------|--|
|                           | Yrs. of<br>Exposure    | No. of<br>Recurs | Recurs per<br>100 Years of<br>Exposure | Yrs. of<br>Exposure        | No. of<br>Recurs | Recurs per<br>100 Years of<br>Exposure |
| 1-5 mos.                  | 26.2                   | 3                | 5                                      | 91.9                       | 11               | 11.6                                   |
| 6-12 mos.                 | 3.7                    | 3                | 8.0                                    | 92.1                       | 13               | 14.1                                   |
| 1-2 yrs.                  | 127.0                  | 3                | 2.3                                    | 267.0                      | 14               | 5                                      |
| 3-4 yrs.                  | 83.5                   | 3                | 3.5                                    | 161.0                      | 3                | 1.8                                    |
| 5-9 yrs.                  | 110.0                  | 2                | 1.8                                    | 11.0                       | 8                | 7.1                                    |
| 10-19 yrs.                | 48.0                   | 1                | 2.1                                    | 7.0                        | 1                | (13.3)                                 |
| Total                     | 497.4                  | 14               | 3.2                                    | 734.3                      | 50               | 6.8                                    |

gives the rate as calculated from all the cases of reinfarction, 427 in number while the second rate is calculated from the 324 patients whose first infarct was included in the basic series for the present study. The first rate is possibly more suited for comparing with rates from other series. The other rates in the table are taken from Wright et al. (1954). The rates agree well, especially the rate for the present series and for the series of Doscher and Poindexter (1950).

Bjerkelund (1957) used a more ingenious method of estimating the risk of reinfarction. He calculated the probability at various times after the infarct that another infarct will occur or what he called the force of recurrence. Table 61 shows the force of

recurrence in 907 or 94.2 per cent of the Malmö patients from 1935 through 1954 who survived their first infarct by four weeks. It shows the number of recurrences, and the recurrences expressed per 100 person years of exposure at six different intervals after the first infarct in the cases divided by sex and ages above and below 60. Only second infarcts were considered here and as soon as the patient got a second infarct they were excluded from the series. Figure 24 gives the recurrences per 100 years of exposure plotted in curves. As seen there, the risk of a second infarct was greatest during the year after the first infarct, for both sexes and ages, the difference between the risk during this interval and during the others was highly sig-

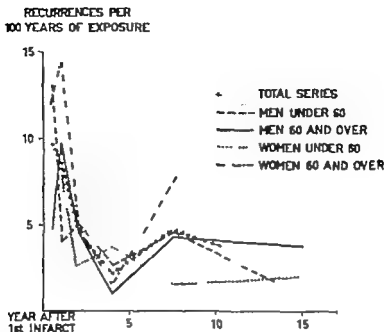


Fig 111 Number of second infarct per 100 years of exposure at different intervals after first infarct in age 60 four week survivors from 1935 through 1954 of different sex and age at first infarction

nificant. Bjerkelund (1957) made the same observation. He found, however that this was mainly caused by the large number of recurrences during the first six months, an observation which only applies to the men under 60 in the present series where the rate was significantly higher than in the next six months. The other groups showed a trend towards the opposite. The men under 60 at infarction ran a slightly greater risk of recurrence than the older men, but the difference was not significant. On the other hand, the women under 60 at infarction ran a significantly lower risk of recurrence than the older women. This is in keeping with the age distributions shown in figure 53.

Bjerkelund (1957) used this method for determining the efficacy of long range anticoagulant therapy. His control series, containing 118 patients, 38 with reinfarcts is best for comparing with the present one, as only a few of the present patients towards the end of the period were given long range anticoagulant therapy. The force of recurrence was higher in every group of Bjerkelund's control series than in the Malmö series. Thus Bjerkelund's patients under 60 showed a rate of 16.7 during the first year as against 7.9 in the Malmö series. The corresponding figures for the older patients were 29.3 against 9.9. It seems that 20 per cent of Bjerkelund's patients with a second infarct were not hospitalized,

ul even when allowance is made for his, his rates are higher than in the Isalmū series. This might be because it was a prospective study directed specially to the diagnosis of reinfarction.

To sum up the series shows that the risk of reinfarction is by far the greatest during the year following a first infarct. It also shows that elderly

women are more subject to reinfarction than young ones but that the opposite may be true of men.

The four week mortality was greater after reinfarcts than after first infarcts. The sexes did not differ in amount of four week mortality after second infarcts, the same as they did not differ in this mortality after first infarcts.

obvious from Ekvall's (1955) analysis of the relationship between the time of hospitalization and the short term mortality. Ekvall found that 67 out of 212 patients hospitalized within four weeks or 32 per cent, died within four weeks of admission. This rate is like that in the Malmö series one would not have expected this, for only 29 per cent of Ekvall's patients were admitted within 24 hours 43 per cent within 48 hours and 57 per cent within 3 days, as against 62, 70 and 74 per cent within the same periods in the present series.

To sum up it was impossible to determine how many patients with myocardial infarction were missing from the series. Because of the conditions in Malmö the present series is probably more representative of the cases of myocardial infarction diagnosed in routine medical practice in Malmö than most hospital series are of their underlying populations.

#### MYOCARDIAL INFARCTION IN OLD PATIENTS

Table 4 giving the ratios between men and women at different ages in the present series, shows that the men greatly outnumbered the women among the young patients but as the patients grew older the preponderance of men became smaller and after the age of 70 there was one woman to every man. This does not mean that old women are as liable to myocardial infarction as are old men. There are more old women in the general population than there are old men and figure 8 indicates that compared with

the number of same-sexed same aged persons in the underlying population, old men continue to be more liable to infarction than do old women. It is important to recognize this, for it is often stated that when women grow older they become just as prone as men to atherosclerosis and its different manifestations. Plotz (1957) for example, said after going through the literature on the sex ratio in coronary disease that in old age the two sexes were equally vulnerable.

It is still a matter of hypothesis why men are more prone than women to myocardial infarction and coronary heart disease. Dock (1963) has recently published a survey of the theories and a list of the latest references.

Several authors state that myocardial infarction is most apt to occur between the ages of 50 and 69 and after that less frequently. Doscher and Poindexter (1950) and Wright et al (1954) found that persons in their 50's were most vulnerable, while Mintz and Katz (1947) found that persons in their 60's were most vulnerable, as did also Eckerström (1951) and Ekvall (1955). Judging at first sight from the present series the men were most liable to infarction in their 60's and the women in their 70's. After the figures were projected against the underlying population, however the men also proved to be most liable in their 70's.

Thus the same was noted in the Malmö series as by others (e.g. Peel 1955) that the liability to infarction rose with advancing age up to a cer-

tain time of life and then fell. Here the peak frequency was noted in the 6's others have reported other ages to be most vulnerable. This observation of a drop in frequency of myocardial infarctions in old people is puzzling for international statistics show a rise in the frequency of death from coronary heart disease with aging right up to the end (Schettler 1961). It may be that the drop in the rate of myocardial infarction in elderly people so many have observed does not reflect the true circumstances. In the first place many old patients die soon after the infarction starts. Thus probably more of them die before they reach hospital than do younger patients. Secondly there is a small rise in the rate of painless infarction with advancing age. As private practitioners without an electrocardiograph often have no other symptoms than pain to go by they are probably more apt to miss the diagnosis when the patients are old. Thirdly it is also possible that some extremely old patients are not sent to hospital even if the physician suspects or knows they have a myocardial infarct. It is not impossible, therefore, that the drop in the rate of hospitalized patients among the old does not reflect the true frequency of myocardial infarction among them.

#### MYOCARDIAL INFARCTION IN YOUNG PATIENTS

To go to the other end of the age scale, the youngest patients in the series differed surprisingly from the others in several respects. While the four week

mortality rate was closely related to the age at infarction from the age of 40 on (fig 30) the patients under 40 had a rate of 30.3 per cent which was higher than that of the 50 year olds. Secondly the patients under 40 had a relatively poor long term outcome. Thirdly they had antecedent angina pectoris just as often as the older patients, though usually not for as long a time. Fourthly they seemed to show a large number of old, healed infarcts on autopsy. Many of them also had antecedent hypertension, but this was to be expected from reports in the literature.

Because of this, I shall analyze these young patients a little more closely. The series contained 38 cases of a first infarct in patients under 40 including 33 men and 5 women.

One of the women had had diabetes for 20 years when she got her infarct at the age of 38. Another aged 34 had chronic nephritis with hypertension. If it is true as supposed, that diabetes, hypertension and obesity as well as hypercholesterolemia and hereditary loading predispose a person to coronary heart disease, there were predisposing factors in these two cases. A third woman aged 35 had combined mitral stenosis and insufficiency as the result of rheumatic fever the infarct in her case was assumed to be due to an embolus the patient died three years later from decompensation, but unfortunately permission for autopsy was denied. A fourth, aged 39 had been excessively obese and had gone down 42 Kg by dieting and taking thyroid compounds during a

couple of years before her infarct whether her obesity or dieting had anything to do with the infarct is obscure. In the case of the fifth woman, aged 38 nothing in the clinical condition or past history pointed to complicating or predisposing disorders.

Nine of the 33 men under 40 were hypertensive. Another 6 had abnormally high cholesterol values. One had diabetes mellitus. In 3 cases there was a family disposition to coronary heart disease. These 3 will now be described in more detail.

Two of the patients were brothers. Their father died of a "heart attack" when he was 43. One of the brothers got his infarct when he was 31, the other when he was 32. One of them had a normal cholesterol level, the other was not examined for cholesterol. The 32 year old died suddenly, 24 hours after the onset of the infarct and autopsy revealed thin transparent coronary arteries of normal width, and an atheromatous plaque bulging into the descending branch of the left coronary artery to which a fresh thrombus was attached.

The third patient was a man of 39 whose father died of a heart attack when he was 45. Two paternal uncles also died of a heart attack. The father's other siblings were said to have angina pectoris. The patient was the youngest of six, and all his siblings had medically diagnosed angina pectoris. The patient himself had hypercholesterolemia, as did also other members of his family.

Thus 19 or more than half the 33 men had one of the disorders that are

thought to favor the development of coronary heart disease and myocardial infarction. Another man had syphilis and this may have been what caused the infarction, though it could not be proved. Another man had been hospitalized six times for deep and superficial thrombosis in his legs with emboli during the four years before he was admitted with typical signs of infarction. Three years later he died. No atherosclerosis was discovered on autopsy but the foramen ovale was patent and the descending branch of the left coronary artery was completely blocked and the corresponding area in the myocardium showed evidence of healed infarction interpreted as due to an embolus. There were no predisposing factors in the remaining 12 cases.

Old hospital records are not reliable for judging the frequency of predisposing factors in patients of different ages. The younger the patients are when they get an infarct, however, the more interested the attending physicians are in predisposing factors, and the records of young patients are probably more detailed in this respect than the records of older patients.

Most of the infarcts in the patients under 40 were of atherosclerotic origin. Two may have been caused by an embolus and 1 patient had syphilis, though it could not be established that it had caused the infarct. The only explanation for the rest of the cases. So out of 38 was atherosclerosis, and the autopsies done revealed atherosclerotic changes in the coronary arteries.

Infarction of embolic origin is thought to be more often lethal than infarction of atherosclerotic origin (Schrader et al., 1956). This may be so but it is hard to know whether an infarct is of embolic origin while the patient is alive. Thus it may be that cases of this origin are missed if the patient survives the acute phase with the result that infarction of this origin is thought to cause more deaths than it actually does. One would expect a larger proportion of infarcts of embolic origin in young than in older patients but only 2 of the patients under 40 in this series had histories which pointed to this origin, and both of them survived the first four weeks. In other words, the unexpectedly high four week mortality in the young patients cannot be explained by many of them having infarcts of embolic origin.

There are other reasons why young people might more often die after an attack than older people. It may be that young people are particularly prone to other disorders which decrease the chances of survival. The poor prognosis for young patients, especially in the long run, would then be caused by the risk of death associated with these disorders being added on to the risk of death associated with the infarction itself. Another explanation might be that atherosclerosis runs a more rapid course in young persons than later in life. This would explain why they had a worse long term outcome and why they had a shorter history of angina pectoris on the average. It might also explain their lower

four week survival rate if it is so that there is not so much chance of a collateral coronary circulation developing when the disease runs a rapid course.

The terminal causes of death in the acute stages of myocardial infarction are roughly cardiac decompensation, lethal disorders in cardiac rhythm, cardiac rupture and other disorders not directly connected with the heart. Several authors have tried to determine the frequency of different terminal causes of death. As would be expected they agree on the whole about the frequency of rupture (chap. 8) but they disagree about the frequency of cardiac decompensation and disorders of rhythm. Hellerstein and Turell (1958) found that 39.7 per cent of 73 patients who died, died from disorders in cardiac rhythm while Ball et al. (1953a) found that 2 out of every 3 persons dying from purely cardiac reasons died from ventricular fibrillation. McQuay et al. (1955) said that myocardial failure caused the death in 45 per cent of 133 patients dying in the acute phase of myocardial infarction, and what they called coronary failure in another 23 per cent.

Ten of the patients under 40 in the present series died in the acute phase of infarction. Two died suddenly without warning which points to a disorder of rhythm, either ventricular fibrillation or asystole. As many as 7 died from cardiac decompensation. The records in the tenth case do not permit any conclusions concerning the final cause of death. There was no instance of cardiac rupture in this age



group. It is surprising in view of what is said in the literature that only 2 out of the 9 patients in this group whose terminal cause of death was established, died from a disorder in rhythm. The cases are too few, however, to allow any conclusions. It is also hard to compare different series for this feature, for one cause of death does not exclude the other. What cause of death should be chosen, for example, when a patient who shows severe clinical signs of cardiac decompensation dies from ventricular fibrillation?

During recent years new methods have been evolved that increase the chances of saving patients who get disorders in rhythm that before would inevitably lead to death. These are cardiac massage, and the use of defibrillators and pacemakers. It is not sure how large a proportion of the deaths soon after the onset of myocardial infarction are caused by disorders in cardiac rhythm, but there is reason to hope that the proportion will decrease with these new aids to treatment.

## SUMMARY

This study attempts to answer three questions: 1. What are the characteristics of patients clinically diagnosed as having myocardial infarction? 2. What are the characteristics of the onset and acute stage in these cases? 3. What is the short term outlook for the patients, and what is the long term outlook for survival and functional recovery for the ones who survive the first four weeks?

The main study is based on all the cases of recent myocardial infarction treated at the Medical Department in Malmö from 1935 through 1959; they amounted to 2,904. The diagnosis of recent myocardial infarction was made from the clinical laboratory and electrocardiographic data in the records of the patients. The criteria used are described and discussed.

The city of Malmö, which now has more than 225,000 inhabitants, has only one hospital, and the 2,904 cases represented 97 per cent of all the cases of recent myocardial infarction hospitalized in the city during these 25 years. As reliable vital statistics are available for Malmö, the observations made in the cases of myocardial infarction could be projected against the

population in general. The observations cannot be compared directly with ones obtained from prospective population studies. The reasons why they cannot are discussed in detail.

For the analysis of most characteristics the 2,477 cases given the clinical diagnosis of a first infarct were used, for some characteristics only the 1,541 first infarcts from 1935 through 1954. The 427 cases of a reinfarct were studied separately for certain features. In addition to these 2,904 cases from 1935 through 1959, 132 cases from 1961 and 1962 were used for a special study of the effects of steroid therapy and to get further data on a number of laboratory features. Thus the total number of cases studied amounted to 3,036.

The patients were 64 years old, on the average, the men 61 and the women 68. There were altogether 1.8 men to every woman. Among the patients in their 30's the ratio was 0.6:1, but the difference decreased with aging and after the age of 60 there was one woman to every man. When the data from these cases were projected against the statistics for the general population, however, it was

others their age. For example the men in their 40's surviving the first four weeks ran about six times as great a risk of dying within five years as did men of the corresponding age in the general population. Patients getting infarcts in their 80's ran about the same risk of dying after the first four weeks as did people their age on the whole. The men and women did not differ significantly in long term survival but the women showed a tendency to a worse prognosis in the long run. Antecedent diabetes mellitus and hypertension had an unfavorable effect on the long term outcome. The diabetic patients did not have a worse long term outcome than could be expected from their having diabetes in addition to myocardial infarction. The long term prognosis in the four week survivors seemed to be slightly worse if the infarct was severe than if it was mild.

Patients with angina pectoris before their infarct were more apt than the others to have it later on, and to have it more severely. Patients over 60 at the time of their infarct were less apt to have angina pectoris after their infarct than patients getting their infarcts before 60 and more apt to have it in milder form than the younger patients.

Altogether 44 per cent of the patients re-examined in 1967 then belonged to functional group I (as defined by the New York Heart Association) and 34 per cent to group II. The long term functional capacity was not affected by sex or class of infarct. The distribution into different

functional groups was the same whether the patients were under or over 60 when they got their infarct.

The amount of work the patients did after their infarcts depended greatly on how old they were at the patients getting their infarct before they were 50 went back to their old work after 50 less and less did so and only 17 per cent of the patients getting their infarcts in their 70's went back to work.

Altogether 811 or 95 per cent of the 858 patients dying within the first four weeks of what was clinically judged to be a first infarct were autopsied. In no less than 74 per cent of these 811 signs of old and healed infarction were then discovered in addition to the fresh infarct for which they were hospitalized. This 74 per cent included more men than women. It also included an unexpectedly large number of patients under 50. These observations are discussed in detail.

Cardiac rupture was observed in 13 per cent of the autopsies. The rate increased with the age of the patient and was higher in women than in men. Seventy five per cent of the ruptures occurred within the first week of the infarct the rate was highest the first 24 hours and then dropped successively.

The risk of recurrence after a first infarct was much greater the first year after than it was later. Women over 60 were more prone to reinfarction than younger women but the reverse seemed to be true of men. The four week mortality after the reinfarct was higher than after the first

infarcts and was the same for the men and women.

There was a steady rise during the years 1931 through 1959 in the number of patients with infarcts admitted to the Department. After various forms of analysis to try to find external

causes for this rise it was concluded that during the 1950's at least there had been a genuine increase in the number of hospitalized cases of myocardial infarction in the city of Malmö.

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# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 407

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## N EPIDEMIOLOGICAL STUDY OF HIGH BLOOD PRESSURE

*with Special Reference to the Influence of Blood Pressure  
and Age on Cardiac Signs and Symptoms*

BY  
SIGURD BJ. HUMERFELT

ACCOMPANIES VOL. 175

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BERGEN 1963







FROM THE UNIVERSITY OF BERGEN SCHOOL OF MEDICINE  
MEDICAL DEPARTMENT A (O J BROCH, M D.)

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# An Epidemiological Study of High Blood Pressure

*with Special Reference to the Influence of Blood Pressure  
and Age on Cardiac Signs and Symptoms*

By

SIGURD BJ HUVERFELT

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## Preface

A new technique in clinical research has been developed during the last decades. It consists in the study of disease, not in individual patients, but in groups of individuals based on populations of normal composition including the sick and the healthy as they are found in the community. In research on hypertension such epidemiological surveys have been highly recommended.

This survey is based upon groups of individuals randomly selected from the Bergen series previously published by J. B  , Fr. Wedervang, and myself in 1957 and it serves as a supplement to that investigation. The selected series is based on group I covering the northern and central parts of the city and I started the survey parallel with the Bergen investigation. I was greatly encouraged to start this investigation by my former teacher and friend the late Professor Dr. med. H. Rasmussen, who started and was in charge of the Bergen series until the material had been collected. I owe my greatest debt of gratitude to him.

After his sudden death, his successor Professor Dr. med. O. J. Broch encouraged me to continue the investigations, and I am particularly grateful for his advice at all stages of these studies.

I am also greatly indebted to my previous joint authors, Professor Dr. med. J. B   and Docent Fr. Wedervang, Ph. D. for their valuable advice in the first important stages of the survey.

The Bergen series made use of casual blood pressure readings, and one of the

objects of this investigation is to study the variability of the blood pressure in relation to age and sex when it is taken again after rest. Secondly the subjective symptoms and objective findings indicative of cardiac disease have been recorded with the main object of seeing whether they show any quantitative or qualitative relationship to blood pressure and age.

As the survey advanced, several questions regarding the appropriate statistical methods arose and the need for mathematical and statistical advice was obvious to me, a clinician, starting the survey as a recruit in the field of epidemiology. Therefore the investigation has been in progress for a comparatively long period of time. The work had also to be done during intervals between other pressing tasks.

I am greatly indebted to all who have given me advice. I am particularly grateful to Professor C. L. Godake, Ph. D. and his group at the Geophysical Institute, for valuable assistance especially to Mr. K. Fl  sand for his comprehensive work in carrying out nearly all the statistical calculations in chapters V-VII to Mr. J. B. Hann  dal for his handling of the data, and to Mr. E. Bolstad for his assistance in drawing the figures.

Furthermore I am most grateful to Professor E. Sverdrup, Ph. D., University of Oslo, for his advice concerning the method to be used in the binomial distribution (chapter VII) and to Professor Peter Armitage, M. A., Ph. D., Department of Medical Statistics and Epidemiology, London School of Hygiene and



Tropical Medicine, for his advice on the appropriate methods in the heart volume determinations (chapter VIII)

I also wish to thank Professor D D Reid for his help in admitting me as a student from January to September 1961 at The Department of Medical Statistics and Epidemiology London School of Hygiene and Tropical Medicine where I received excellent training in the field of epidemiology

I am also indebted to the Medical Officer of Health of Bergen E. Ørnevad M D the Head of the Department of Preventive Medicine E. Eilertsen M D., and the City of Bergen Statistics Bureau for their help in supplying me with all the data I needed. Special thanks are due to P St. Aubin M D., U.S.A. for his assistance in assessing the observer variability in reading the X rays.

Furthermore, I should like to thank Professor Dr med. Tr Gjestland and Knut Westlund M D., Oslo, for their valuable

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Special thanks are due to Bjørg Løvås, B R.N and Turid Ørnevad S R.N. and several students for their skilled and conscientious assistance while the examinations took place.

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## CHAPTER I

### Introduction

It is well known that in Norway as in most lands that are well developed technically and economically a distinct fall in the death-rate has occurred in the last 3-5 decades. The investigations made by Ström (223) in this country show that the general (total) mortality was 20 ‰ lower in the 4-year period 1949-52 than in the 4-year period 1929-32. During this time the death-rate fell from 10.88 to 8.75 per thousand of the population. The fall was practically the same for men as for women, 19.1 and 19.5 respectively. The drop in total mortality is even more marked if we go further back in time: thus in the 10 years 1911-20 the average death rate was 13.77 per thousand inhabitants.

This fall in the total mortality shows a marked difference in the different age groups. Thus there is a marked fall in the death-rate in childhood (40-70 ‰) and youth (70-80 ‰) while in the higher age groups the drop is less pronounced.

But this fall in death-rates does not apply to all illnesses. If one compares the mortality statistics for the year 1910 (36) to those for the year 1959 (38) a marked fall in the mortality from infectious diseases is demonstrated, while there seems to have been an increase in the death-rate from cardiovascular and renal diseases. In other words, in a lifetime the pattern of diseases has altered and the risk of illness and death has shifted from the young to the middle-aged and elderly most pronouncedly in men.

Cardiovascular and renal diseases form

a heterogeneous group including different types of heart diseases, intracranial lesions of vascular aetiology and all forms of nephritis. According to Leavell & Clark (118) this group represents the end result on heart, intracranial blood vessels and kidneys of a number of different pathological processes.

These diseases accounted in all for 176 deaths per 100 000 lives in 1910 while in 1959 (1958 values in parentheses) 433 (435) deaths in men and 425 (436) deaths in women per 100 000 occurred. This corresponds to 47 ‰ (48 ‰) of all deaths.

According to the reports from the Central Bureau of Statistics in Norway (37) a distinct difference is noticeable in the mortality within the different age groups during the last 25 years. The mortality among men in all groups over 40 years has increased markedly since World War II while in women under 60 years of age a decrease is seen. Thus the excess mortality in men under 60 years of age is still further marked.

In relation to the total mortality cardiovascular and renal diseases are the most common cause of death in our society today. But the question arises whether this increase is real. There are many factors which in part explain the increase in mortality from cardiovascular diseases. Firstly the increase has been associated with the ageing of the population. In Norway in 1921 the life-expectancy was 60 years for men and 64 years for women, while by 1951/55 this had increased to an

average of 71.1 years for men and 74.2 years for women. It is therefore natural that many individuals die as a result of cardiovascular disease.

Because of the definite difference in social and health conditions in preceding decades and the improvement in diagnostic possibilities one must be cautious in the use of mortality statistics when comparing the different periods of time, and particularly careful if one wishes to compare the incidence of the different entities within cardiovascular disease.

In this country the mortality statistics from before 1951 lack an aetiological classification. Therefore one cannot determine the frequency of hypertension and hypertensive diseases, or whether they present cardiac, cerebral or renal manifestations. But from the introduction to the International Lists of Diseases and Causes of Death (741) in 1951 it is possible to determine the different aetiological types of cardiovascular diseases.

According to the latest available data from Norway (37) 14 095 persons died in 1937 from cardiovascular and renal diseases. Table 11 gives the sex and age specific death rates for the various groups of diagnoses.

Diseases of the heart and other diseases of the circulatory system (400-468) accounted for 63% of the cardiovascular deaths. Vascular lesions of the central nervous system (330-331) accounted for 31% while the rest (3%) included chronic nephritis (59%), congenital malformation (754) and cardiovascular syphilis (022-073).

Within the group diseases of the heart and other diseases of the circulatory system (400-468) hypertension (440-447) accounts in all for 79 deaths per 100 000 in women and in all 20 deaths per 100 000 in men. Deaths from hypertension show a marked increase with age in both sexes. There is, however, a slight difference between the two sexes. Death from hypertension occurs more often in men under 40 years of age while over

70 years of age it is more frequent in women.

One of the main difficulties with the mortality statistics is that the diseases may be reported as the underlying cause of death as a complication or as a contributory condition. Thus in Norway in 1937 in addition to the 14 095 deaths from cardiovascular and renal disease, 3 703 (26%) were reported as complications of other cardiovascular conditions and 2,142 deaths (15%) were reported as complications or causes contributory to other underlying causes of death.

Within diseases of the heart and other diseases of the circulatory system there is a marked difference in the frequency of reporting the various combinations of multiple causes. While hypertension with heart disease (440-443) is reported as the underlying cause in 72% and as a complication to another cardiovascular death in 20% the corresponding figures for hypertension without mention of heart (444-447) are 10% and 83% respectively. The remainder include complications to other underlying causes. On the other hand, coronary disease and infarction (420.1 & 2) are reported as the underlying cause in 94% (see Table 1.2).

Although these mortality data give some idea of the importance of hypertensive disease in relation to other heart diseases and other underlying causes of death, it is a poor index of the incidence of hypertension. Hypertension and hypertensive disease are not precisely defined. There are no uniform criteria and the question of its exact extent is still unanswered (see p. 20). Therefore mortality statistics do not give sufficient information on the importance of hypertension and hypertensive disease. Adequate morbidity records and clinical records of patients attending hospital may be used to measure the incidence of disease.

Valuable morbidity statistics have hitherto been difficult to obtain in this country. But since July 1956 the total population has been insured and it should now be

Table 11 Mortality from cardiovascular diseases by groups of diagnoses 1957

| I (ter<br>national)<br>No. | Diagnosis  | Per 100,000 population |       |       |       |       |       |       |       |       |       |       |       |       |       |
|----------------------------|--|------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                            |  | Females                |       |       |       |       |       |       | Males |       |       |       |       |       |       |
|                            |  | 0-39                   | 40-49 | 50-59 | 60-69 | 70-79 | ≥ 80  | Total | 0-39  | 40-49 | 50-59 | 60-69 | 70-79 | ≥ 80  | Total |
| 350-354                    | Vascular lesions of central<br>nervous system                      | 2                      | 17    | 53    | 224   | 1,051 | 5,242 | 154   | 2     | 16    | 51    | 259   | 1,005 | 2,870 | 119   |
| 400-402                    | Rheumatic fever  |                        | 1     |       | 1     |       | 5     |       |       |       | 1     | 1     | 3     |       |       |
| 410-416                    | Chron. rheumatic heart<br>disease                                  | 1                      | 10    | 25    | 90    | 67    | 76    | 13    | 1     | 10    | 13    | 37    | 41    | 43    | 9     |
| 420.1                      | Coronary disease   |                        | 8     | 47    | 197   | 572   | 1,059 | 77    | 2     | 53    | 211   | 340   | 970   | 1,280 | 140   |
| 420.0                      | Ischaemia  |                        |       |       |       |       |       |       |       |       |       |       |       |       |       |
| 420.2                      | Other arterio-vascular<br>and degenerative heart<br>disease        |                        |       | 9     | 79    | 491   | 2,160 | 80    |       | 10    | 22    | 117   | 538   | 1,891 | 67    |
| 421-422                    |  |                        | 3     | 9     | 38    | 197   | 521   | 27    |       | 6     | 13    | 65    | 180   | 441   | 25    |
| 430-434                    | Other diseases of heart  |                        |       |       |       |       |       |       |       |       |       |       |       |       |       |
| 440-443                    | Hypertension with heart<br>disease                                 |                        | 1     | 9     | 53    | 205   | 366   | 25    |       | 1     | 13    | 11    | 161   | 261   | 17    |
| 444-447                    | Hypertension without<br>mention of heart<br>disease                |                        | 2     | 2     | 8     | 29    | 81    | 4     |       | 3     | 3     | 7     | 16    | 65    | 3     |
| 450-456                    | General arterio-vascular<br>and other diseases of<br>arteries      |                        | 1     | 2     | 10    | 81    | 830   | 23    |       | 1     | 4     | 13    | 69    | 920   | 20    |
| 460-468                    | Diseases of veins and<br>other diseases of circula-<br>tory system |                        | 1     | 1     | 7     | 19    | 30    | 3     |       | 1     | 1     | 6     | 15    | 20    | 2     |
| 400-468                    | Total  | 1                      | 27    | 101   | 423   | 1,651 | 5,111 | 252   | 3     | 85    | 781   | 811   | 2,020 | 4,939 | 281   |
| 022-023                    | Cardiovascular syphilis  |                        | 1     | 2     | 2     | 10    | 5     | 1     |       | 1     | 4     | 13    | 24    | 7     | 3     |
| 754                        | Congenital malformation<br>of circulatory system                   | 6                      | 1     | 1     | 1     | 1     |       | 4     |       | 6     | 1     | 1     | 1     |       | 4     |
| 592                        | Chronic nephritis  | 2                      | 5     | 7     | 15    | 29    | 41    | 6     | 3     | 7     | 17    | 19    | 33    | 64    | 9     |

From: Central Bureau of Statistics of Norway Medical Statistical Report 1957



Table 1. Deaths recorded among students when shown as reported on the death certificates in 1957

| Diagnosis                                | International No. | Registred certificate no. |   |                      |   |       | Percent registered |    |    |
|--|-------------------|---------------------------|---|----------------------|---|-------|--------------------|----|----|
|  |                   | Un-lying cause            | Un-lying cause with mention of another underlying cause (100-101) | Sample heart disease | Control cause in other underlying cause | Total | 1                  | 2  | 3  |
| Ischaemic diseases of heart              | 790-791           | 1702                      | 781   | 225                  | 102                                     | 3970  | 100                | 15 | 3  |
| Myocardial infarction                    | 100-101           | 101                       | 11  |                      | 22                                      | 134   | 100                | 7  | 3  |
| Coronary thrombosis                      | 120-121           | 3917                      | 100   | 101                  | 61                                      | 4199  | 100                | 3  | 1  |
| Coronary atherosclerosis                 | 122               | 159                       | 51  |                      | 11                                      | 221   | 100                | 12 | 11 |
| Coronary thrombosis with atherosclerosis | 123               | 2102                      | 75  | 10                   | 321                                     | 3418  | 100                | 25 | 11 |
| Other diseases of heart                  | 102-103           | 1099                      | 100   | 202                  | 217                                     | 1618  | 100                | 10 | 15 |
| Myocarditis                              | 110-111           | 736                       | 700   | 1                    | 102                                     | 1540  | 100                | 20 | 10 |
| Myocarditis with atherosclerosis         | 111-112           | 152                       | 155   | 13                   | 100                                     | 420   | 100                | 83 | 1  |
| Coronary thrombosis with atherosclerosis | 113               | 65                        | 313   | 1                    | 211                                     | 1080  | 100                | 52 | 15 |
| Other diseases of heart                  | 114-115           | 19                        | 137   | 61                   | 70                                      | 313   | 100                | 10 | 0  |
| Thrombosis of arteries                   | 116               | 31                        | 111   | 155                  | 5                                       | 302   | 100                | 12 | 47 |
| Thrombosis of veins                      | 117-118           | 4                         | 31  | 30                   | 11                                      | 121   | 100                | 10 | 25 |
| Other diseases of circulatory system     | 119-120           | 9315                      | 3703  | 619                  | 120                                     | 14757 | 100                | 25 | 4  |
| Myocardial infarction                    | 791               | 138                       | 1   |                      | 25                                      | 164   | 100                | 1  | 15 |
| Coronary thrombosis                      | 122-123           | 679                       | 1   |                      | 5                                       | 786   | 100                | 3  | 1  |
| Coronary atherosclerosis                 | 124               | 1079                      | 17  | 31                   | 6                                       | 1123  | 100                | 11 | 2  |

1. and Centre of Statistics of Norway Medical Statistical Report 1957

possible to obtain information on the morbidity from the different types of cardiovascular disease.

But the validity of these data is questionable. The findings are only given for members who have received sickness benefit or hospital treatment, and no information is given about their relatives who are also covered. Furthermore the doctors mainly give tentative or group diagnoses. Therefore the diagnoses are generally less reliable than those recorded on the death certificates.

The morbidity data from the Bergen Trygdekasse (Health Insurance) in 1957 (23) show a higher incidence of all types of cardiovascular diseases in men in all age groups except 31-40 years of age (see Table 1.3 overleaf).

But essential hypertension is only reported more frequently in men under 40 years of age. The number of days off work (3 consecutive days or longer) from hypertension shows the same trend and is also reported more frequently in the young men. In other words illness from hypertension seem to be more frequent in women in the other age groups.

Furthermore, of all types of cardiovascular diseases the proportion of illness and of mortality that is charged to hypertension is different. While the over-all incidence of illness from hypertension in Bergen is about 25% of all types of cardiovascular diseases in women and 12% in men (Table 1.3) the corresponding figures from the mortality rates in Norway (Table 1.1) are 7% and 3% respectively. Using the mortality figures from Bergen 1959 (22) the proportion is very nearly the same (7.8% and 5% respectively). This seems to indicate that hypertension is relatively less important as a cause of death than as a cause of illness. Mortality statistics can provide a direct measure of the incidence of disease only for those diseases which have a high mortality rate (see Doll, 31).

During the last 10-20 years, multiple series, from the industrial and public

health officers have been collected in this country. However no information on hypertension as a cause of illness has hitherto been published.

The clinical records of patients attending hospitals also have the advantage that they can provide data on conditions with a low fatality. However it is seldom possible to relate the numbers of patients treated to a known population, and hence it is usually not possible to calculate accurate incidence rates. This applies to the records from the University Hospital in Bergen. A grouping of the diagnoses made at the Medical Department A from 1950-54 shows that cardiovascular and renal diseases came to 44% of 12,516 admissions during this 5-year period. Hypertension accounted in all for 21% of all types of cardiovascular disease (men 15% and women 27%) and hypertensive heart disease accounted for 29% of all types of heart disease (men 21% and women 36%).

These over-all figures are fairly close to the morbidity data from the Bergen Trygdekasse (Health Insurance). But a closer study of the data, related to age is not possible without investigating all the hospital records.

In this introductory chapter only a few series from this country have been mentioned. It should be emphasized that more valuable information on the frequency of hypertension as a cause of illness is given in several papers from other countries, for example by Collins (41) from the U.S.A., by Logan & Cushion (133) from England and by Jensen (106) from Denmark.

Both morbidity and hospital figures show the same tendency indicating that hypertension is more important as a cause of illness than as a cause of death.

We know that cardiac and vascular complications follow in the wake of hypertensive disease, and it is these complications which are recorded in the mortality statistics (see p. 26). The extent to which high blood pressure is responsible

Table 1.3. *Morbidity from cardiovascular diseases, Bergen Health Insurance data 1957*  
Number of people ill and number of days of illness in relation to age and sex

| Diagnosis | Sex     |  | Females |       |       |       |       |       |          | Males |       |       |       |       |       |          |
|-----------|---------|--|---------|-------|-------|-------|-------|-------|----------|-------|-------|-------|-------|-------|-------|----------|
|           | Age     |  | 21-30   | 31-40 | 41-50 | 51-60 | 61-70 | 71    | All ages | 21-30 | 31-40 | 41-50 | 51-60 | 61-70 | 71    | All ages |
|           | Members |  | 5,282   | 3,680 | 4,389 | 4,678 | 3,048 | 4,158 | 30,115   | 7,670 | 9,171 | 8,160 | 6,846 | 4,818 | 2,938 | 43,559   |

### Number of people ill

|                                     |                  |     |     |      |      |      |      |      |     |     |      |      |      |      |      |
|-------------------------------------|------------------|-----|-----|------|------|------|------|------|-----|-----|------|------|------|------|------|
| Cardiovascular disease<br>all types | No.<br>per 1,000 | 6   | 26  | 54   | 84   | 74   | 100  | 344  | 16  | 48  | 86   | 168  | 158  | 100  | 576  |
|                                     |                  | 1.1 | 7.1 | 12.3 | 18.0 | 19.2 | 24.1 | 11.4 | 2.1 | 5.2 | 10.5 | 24.5 | 32.8 | 33.8 | 13.3 |
| Essential<br>hypertension           | No.<br>per 1,000 |     | 2   | 14   | 28   | 26   | 16   | 86   | 2   | 8   | 2    | 20   | 18   | 8    | 68   |
|                                     |                  |     | 0.5 | 3    | 6    | 6.8  | 3.8  | 2.9  | 0.3 | 0.9 | 0.2  | 4.4  | 3.7  | 2.7  | 1.5  |

### Day of illness

|                                     |                  |    |       |       |       |       |       |        |     |       |       |        |        |       |        |
|-------------------------------------|------------------|----|-------|-------|-------|-------|-------|--------|-----|-------|-------|--------|--------|-------|--------|
| Cardiovascular disease<br>all types | No.<br>per 1,000 | 72 | 1,032 | 2,446 | 4,900 | 8,042 | 3,638 | 20,220 | 330 | 3,662 | 6,605 | 14,995 | 14,442 | 4,090 | 44,126 |
|                                     |                  | 14 | 280   | 537   | 1,066 | 2,089 | 875   | 671    | 43  | 399   | 803   | 2,189  | 2,997  | 1,382 | 1,015  |
| Essential<br>hypertension           | No.<br>per 1,000 |    | 2     | 788   | 1,620 | 4,196 | 984   | 7,592  | 56  | 298   | 1,460 | 1,034  | 1,060  | 882   | 4,790  |
|                                     |                  |    | 0.5   | 180   | 346   | 1,090 | 237   | 252    | 7.3 | 32    | 178   | 151    | 220    | 298   | 110    |

Total members includes the age group 15-20 years of age.

From Melding for Bergen Trygdekasse for Årene 1935-1956-1957 Bergen 1959 Håndskriftarkivet A.3.

for the cardiovascular disease and death, however, is not yet established. Investigations into the relationship between elevated blood pressure and the frequency of hypertensive heart disease in general are very much needed.

### Summary

Although a distinct fall in the over all death-rate has occurred in the last 3-5 decades in Norway there seems to have been an increase in the death-rate from cardiovascular and renal diseases, most marked in men in all age groups over 40 years. Because of the ageing of the population, the difference in social and health conditions, and the improvement in diagnostic possibilities, one must be cautious in the use of mortality statistics when comparing different periods of time. When determining the different aetiological types of cardiovascular diseases in the mortality statistics from recent years, the difficulty is that the disease may be reported as the underlying cause of death as a complication, or as a contributory condition. Thus there is a marked difference in the frequency of reporting hypertension in relation to other heart diseases and other underlying causes of death. Therefore mortality statistics are a poor index of the incidence of hypertension. Hypertension and hypertensive disease are not precisely

defined. There are no uniform criteria and the question of their exact extent is still undetermined.

Reliable morbidity statistics have hitherto been difficult to obtain in this country. The morbidity data from the Health Insurance only give the figures for members who have received sickness benefit or hospital treatment, and no information is given about their relatives who are also covered. Furthermore the doctors mainly give tentative diagnoses.

When using clinical records of patients attending hospitals or out-patient clinics it is seldom possible to relate the numbers of patients to a known population, and hence it is usually not possible to calculate accurate incidence rates.

However both the morbidity figures from the Bergen Health Insurance and hospital figures from the University Hospital in Bergen show the same tendency indicating that hypertension is more important as a cause of illness than as a cause of death.

We know that cardiac and vascular complications follow in the wake of hypertensive disease, and it is these complications which are recorded in the mortality statistics.

The extent to which high blood pressure is responsible for the cardiovascular diseases and death, however, is not yet established.

## CHAPTER II

# High blood pressure

### General survey and review of the literature

In the introductory chapter an attempt has been made to stress the importance of cardiovascular and renal diseases in mortality and morbidity statistics. Among cardiovascular and renal diseases those conditions which are accompanied by a high blood pressure play a prominent part and they predominate in the older age groups.

An abnormal increase in the blood pressure in the arterial system is found in a number of different illnesses. These diseases can produce subjective as well as objective manifestations. When the physician is consulted by a patient with high blood pressure, he will, after a thorough clinical examination, comprising an accurate history and a thorough general examination, first ascertain whether the patient complains of symptoms suggestive of an organic disease. In most cases it is necessary to supplement the examination by electrocardiography by X ray examination of the heart and by ophthalmoscopy. In other cases kidney function tests and tests of endocrine dysfunction need to be done before a definite conclusion can be reached. The physician is constantly confronted with the finding that people with the same raised blood pressure show great differences in clinical manifestations, ranging from minimal to severe, and even to incapacitating symptoms suggesting cardiac, cerebral or renal disease. Master, Garfield & Walters (143) stress that In-

creased blood pressure, in itself is not a disease. It is a sign of some underlying disorder'. It is quite obvious that one can find a considerably raised blood pressure in some individuals who do not show any objective or subjective signs of disease, and in whom the raised blood pressure is thus the only objective finding ('symptomless hypertension').

The raised blood pressure is thus to be looked upon as a symptom which can be assigned to various illnesses of greatly differing aetiology. The classification of hypertension is based on this fact.

### Classification of hypertension

We shall note in this short survey of the literature that it was Bright, in his classic works of 1827 and 1836 who described the pathological anatomy of kidney disease for the first time. He pointed out here, among other things, a marked left ventricular hypertrophy and deduced the following (cit. Pickering, 176) 'This naturally leads us to look for some less local cause for the unusual efforts to which the heart has been impelled'.

Gull & Sutton (88) put forward new views in 1872 in their work *Arterio-capillary fibrosis* where, among other findings, they describe changes in the arterioles of the body and come to the following conclusions: 'This morbid change in the arterioles and capillaries is the primary and essential condition of the morbid state called chronic Bright's disease with contracted kidney'.

Maibomed (136) was one of the first clinicians to make full use of the blood pressure estimated during life, and in 1879 and the following years he published important papers on chronic Bright's disease. He showed that termination by renal failure was only one of the outcomes and that death occurred more commonly from heart failure and cerebral hemorrhage.

Important contributions to our understanding of hypertension have since been made by von Basch (16) Allbutt (4) and Huchard (102) all of whom have pointed out that a raised blood pressure occurs in two states, either with or without kidney disease. Allbutt introduced the term *Hyperpæsis* for the group in which kidney disease cannot be implicated.

The German Frank (73) in 1911 introduced the term *Essentielle Hypertonie* — a term which is still in use. In 1914 Volhard & Fahr (230) published their well known pathologico-anatomical and clinical monograph. Here they introduced a classification with the division of kidney diseases into three groups, and also introduced the term *Maligne Form der Hypertonie* which denoted the distinct serious type of hypertension which leads to destruction of the kidneys and uræmia.

In the last 10-20 years numerous authors have proposed different classifications of hypertension. Thus Page & Corcoran (168) divided it into renal, cerebral, cardiovascular and endocrine forms, together with one of unknown aetiology (*essential* or *malignant hypertension*). They state among other things that, 'It is, however an unpleasant truth that the patients with known or suspected causes for their hypertension constitute only a small percentage of those suffering from arterial hypertension. At least 90-95 percent have the *essential* or *malignant* variety'.

Similarly Fishberg (69) in addition to Schroeder & Steele (203) has put forward a classification that does not deviate greatly from that of Page & Corcoran.

Keith, Wagener & Barker (112) have put forward a classification based on

changes in the optic fundi and on clinical findings. Their classification has been widely used in many clinical works on hypertension, but this is not an aetiological classification either. Similar classifications have been published by many others. For instance Hinton & Lords (99) and Palmer Loolbourov & Doering (169) have drawn up a classification in four groups, based on changes in the optic fundi and involvement of other organs. Smithwick (213) also uses this grouping into four grades on the basis of changes in the organs. Hammarström & Bechgaard (94) have also published a similar classification built up on the subjective symptoms and the objective findings together with electrocardiographic changes, heart size, and changes in the fundi.

Rasmussen (186) in his prognostic study of *essential* diastolic hypertension, came to the conclusion that this large group is made up of conditions with very different organic changes and of greatly varying prognoses. He therefore put forward the following clinical classification based on the organic changes in the heart, brain and kidneys, and also the optic fundi.

1. Mild arterial hypertension (*levis*)
2. Severe arterial hypertension (*gravis*)
3. Malignant arterial hypertension (*maligna*)

The subjective phenomena vary to such a great extent that, according to Rasmussen, they are not suitable as a basis for a classification, and the groupings are therefore based on the objective findings.

Pickering (76) introduced a new factor in his monograph in that he developed a 'two-way classification. The reason for this is that many findings, built up from experimental investigations, pathologic anatomical and clinical observations, suggest that the benign and malignant phases of hypertension are consequences of the intensity of the hypertension, irrespective of the way this is produced.

A benign and a malignant phase can occur in all secondary types of hyper-

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creased blood pressure, in itself is not a disease. It is a sign of some underlying disorder. It is quite obvious that one can find a considerably raised blood pressure in some individuals who do not show any objective or subjective signs of disease, and in whom the raised blood pressure is then the only objective finding ("symptomatic hypertension").

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Any estimate of the frequency of hypertension and hypertensive diseases will be greatly influenced by the criteria selected.

In later years many works have been published which point out that it is artificial to fix a fast and precise borderline for a pathological blood pressure without considering age. These series are based on the blood pressure distribution in the population. The largest and most representative series have been published in the U.S.A. by Master, Dublin & Marks (147) in 1950 and in England by Hamilton, Pickering, Roberts & Sowry (89) in 1954. A detailed report and review of these and previous surveys have been given by Böe, Hummerfelt & Wedervang (30) presenting the Bergen series in 1953.

Furthermore in 1957 Cornstock (44) published a series based upon a 2% sample of the population in Georgia, U.S.A. The blood pressure study was done in 1954-55 8 years after the identification of the base population. Of the 1912 persons in the sample, 70% of them whites, observations were obtained on 1162 (61%). The most serious loss from the sample population was due to emigration and death. In order to obtain blood pressure readings under 'normal conditions' the subjects were examined by 9 examiners, 8 nurses, and 1 physician in their home environment as far as this was possible. This was achieved in the case of 91% of the subjects.

In 1958 Miall & Oldham (151) published the results of surveys carried out in an urban and a rural population in South Wales. Samples were selected at random (1 in 90) from the population, and the measurements were made on 623 subjects in the sample and on 2,245 of their first degree relatives living within 25 miles of each area. This represented over 95% of both the population samples and their relatives. This response rate is remarkably good and the best reported so far in a population sample. Measurements were made under standard circumstances by

one observer and all observations were made in the subjects' own homes at any time of the day.

In 1959 Lin *et al.* (129) published a population series from Formosa based upon blood pressure measurements through census home visits of 9,729 urban Chinese over the age of 15. A comparison with similar studies in the U.S.A. and England showed that Chinese had lower systolic and diastolic pressures in younger age groups in both sexes.

Figure 2.1 (p. 22) taken from Miall & Oldham (151) shows the relationship between the systolic and diastolic pressure and age in some of these surveys.

The Figure shows some homogeneity in the shape of the curves but great differences are found in their actual positions.

The most important findings from all these population studies undertaken in scattered parts of the world are

1. An early increase in the average systolic and diastolic pressure with age in both sexes. The increase is more marked after the age of 40 years.
2. In all populations the blood pressure is lower in young women than in young men and higher in old women than in men, and according to Miall (149) 'the cross-over occurs usually towards the end of the reproductive period'.
3. A wide range of the systolic and diastolic pressures is seen and this range increases with age, especially in women after the age of 40 years.
4. The blood pressure is distributed continuously in the population and there is no natural dividing line between those with high blood pressure and those without.

The population studies show that there is such a pronounced increase and range of blood pressure with increasing age in both sexes that several authors have proposed new limits for the normal blood pressure and new limits for hypertension.

But even if one is inclined to accept these new norms, either in whole or in part,



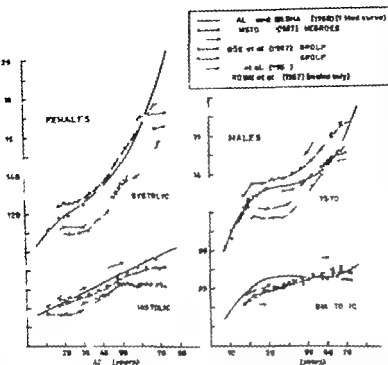


Fig 2.1 The relationships between the systolic and diastolic pressure and age in surveys of representative population samples. Source: Mill, W.E., & Oldham, P.D., Factors Influencing Arterial Blood Pressure in the general Population. Clinical Science. 1958 17 409

one does not escape the fact that the life insurance statistics show figures that suggest that their criteria of a pathological blood pressure cannot be disregarded. Morrell (159) reports that At the level of 140 mm systolic for example, there is a greater percentage of persons with a life expectancy (per age group) below the normal than is to be found at the level of 130 mm systolic. For the insurance company this constitutes a significant risk factor and it must set its standards accordingly. It is as a consequence of these calculations that many authors have fixed a low level as the dividing line between the normal and the pathological. This is most clearly shown in Robinson and Brucer's work (193) based on a statistical study of 7 478 men and 3 405 women selected at random from records of their insurance company and a study of five to ten years continuous records on 500 persons. The authors discarded all subjects with pressures above 140 mm systolic and 90 mm diastolic and regarded the normal

range of systolic and diastolic blood pressure for men and women as 90-120 mm and 60 to 80 mm Hg respectively. On that basis they estimated that slightly more than 40 % of the adult population is either actually or incipiently hypertensive. They consider a blood pressure history of over 120 mm systolic and 80 mm diastolic over a ten-year span in men or women as pathologic. Those with a blood pressure persistently over these values showed a higher mortality rate than those in which the blood pressure was persistently under the same values.

Several life insurance series show the same trends. This is revealed in the earlier actuarial studies by Rogers & Hunter (194 195) and also in new series. The latest available life insurance investigation, involving 3,900 000 lives and 102,000 deaths, from 26 American and Canadian insurance companies, involving persons aged 15 to 69 during the years 1935 to 1953 and published in 1959 (86) shows the following

Table 2. Mortality ratios (per cent) of actual to expected mortality according to systolic and diastolic levels

Males, Policy Issue Ages 15 to 69 Build and Blood Pressure Study Society of Actuaries, 1939

| Systolic BP | Mortality Ratio ( ) | Diastolic BP | Mortality Ratio ( ) |
|-------------|---------------------|--------------|---------------------|
| 88-97       | 78                  | 48-67        | 83                  |
| 98-127      | 88                  | 68-82        | 97                  |
| 128-137     | 118                 | 83-87        | 129                 |
| 138-147     | 155                 | 88-92        | 150                 |
| 148-157     | 194                 | 93-97        | 188                 |
| 158-167     | 244                 | 98-102       | 234                 |
| 168-177     | 242                 | 103-112      | 262                 |

Source: Richard S. Gubner, Life Expectancy of the Young Hypertensive — Hypertension, Recent Advances. The Second Hahnemann Symposium on Hypertensive Disease. Lea & Febiger Philadelphia 1961 p. 22.

The mortality ratio rises progressively with increasing systolic and diastolic blood pressure, beginning with the lowest levels recorded. According to Gubner (86) the untoward effect of blood pressure elevation does not begin at any particular level above the average. Of extreme interest is that the life expectancy in subjects with blood pressure below average values is decidedly better than the life expectancy of the average population and that fewer deaths from cardiovascular disease occur in this group. Each small increment in blood pressure is associated with a progressive increase in the mortality.

Hypertension is not a disease entity but merely a condition which places somewhat greater strain on the cardiovascular system than exists in the average person, producing identical but accelerated and accentuated effects. This concept, presented by Gubner (86) is in full accordance with Pickering and his co-workers view.

But it is not only the prognostic studies of life insurance medicine which show increasing mortality with increasing blood

pressure. Many prognostic studies based on hospital series and out-patients show the same. Mathisen (144) has compiled a review of the different prognostic studies. The series turn out to vary greatly and also show differing results. The Danish series, by Bechgaard (17) is one of the most quoted, and comprises in all 1 038 individuals (325 men and 713 women) referred to the Medical Polyclinic of Rigshospitalet in Copenhagen. These people all showed a blood pressure of 160/100 or 180 mm Hg systolic or higher at the first examination and were followed up for 4-11 years afterwards.

The cause of death was found to be heart disease in 45%, cerebro-vascular accident in 16% and renal insufficiency in 10%. This series gave a relatively good prognosis in the majority of the hypertensive patients. In particular it is to be noted that the prognosis was good for the greater majority of the women, in that the mortality from uncomplicated hypertension was only slightly above that of the general population. The prognosis was worse in men, particularly the younger ones, and the excess mortality was greatest in cases with glomerulonephritis.

The series has been reviewed once again by Bechgaard, Kopp & Nielsen (18) so that the original series has now been followed up for 16-22 years. The results show among other things that as far as the men are concerned, it seems as if only the mildest forms of hypertension leave the possibility of attaining old age, whereas women seem to be able to stand a considerably higher elevation in blood pressure (see Table 2.3).

The mortality in women is normal in the age groups of 50 years and over with a systolic blood pressure below 200 mm Hg, or diastolic below 120 mm Hg. Sixty-three individuals reached more than 76 years of age and 25 more than 80 years in spite of the fact that at the first examination, 20 years previously the blood pressure was 160/100 or 180 mm Hg systolic or higher.



Fishberg (69) proposed the following division of the symptoms

1. Symptoms due to hypertension *per se*
2. Symptoms due to arteriosclerosis.
3. Iatrogenic symptoms.
4. Coincidental symptoms.

Among the truly hypertensive manifestations are some forms of headache, left ventricular hypertrophy and that component of cardiac failure which is not due to coronary arteriosclerosis. Included also are the characteristic manifestations of the malignant phase of the disease.

The nature of the connection between hypertension and arteriosclerosis has not been established, but Fishberg holds that patients with essential hypertension develop, on the average, much more arteriosclerosis than do normotensives of the same age. A high proportion of the cardiac and cerebral manifestations is due to arteriosclerosis, and probably a majority of the patients succumb to them.

Many facts indicate that some of the symptoms are iatrogenic, and Fishberg has found that it is striking how often the patients initial subjective symptoms follow the demonstration of a raised blood pressure when the patient has been informed of the finding. One confirmation of this is to be found in Stewart's investigation (222) of the frequency of headache as a symptom in a series of 200 consecutive cases of severe hypertension, having a diastolic blood pressure of not less than 120 mm Hg with the patient recumbent, after ten minutes rest in that position. He found that headache occurred in 71 of the 96 patients who had knowledge of their hypertension; however of the 104 patients unaware of their hypertension 87 would not admit to having headache. The average diastolic blood pressures of the two groups were fairly close to each other.

Ayman (11) has discussed the hereditary factor in hypertension in several papers, and has put forward the possibility of an inherited specific type of personality. He has further elucidated the symptom-

atology and has come to the conclusion that actually there are probably three groups of symptoms. The earliest group may begin even before the development of significant elevation of the blood pressure, may persist throughout life and later be associated with and overlap the other group of symptoms. This early group of symptoms is due to the psychoneurosis which so often is associated with hypertension.

The next group of symptoms seems to be more clearly related to a vasospasm of the arterioles, associated with rising or markedly high blood pressure levels. Such symptoms consist chiefly of headaches or dizziness and marked tenderness and nervousness. The symptoms of the malignant phase of essential hypertension are, according to Ayman best placed in this group.

The final group of symptoms is of organic aetiology due to permanent damage to the arterioles and viscera, and express themselves in cerebral, cardiac, and renal symptoms.

In a later work Ayman & Pratt (13) suggest that the unspecific psychoneurotic symptoms have hardly any relationship to the raised blood pressure. They state that the psychoneurotic patients without hypertension and of the same age group as the hypertensive patients show the same frequency multiplicity and widespread distribution of symptoms as in the hypertensive patients. It seems however that headache and dizziness occur with slightly more frequency among the hypertensive persons than among the psychoneurotic ones with normal blood pressure. All other symptoms occur in about the same frequency.

Pickering (177) has given a clear account of the various pictures of hypertension. Firstly he points out that arterial disease and high blood pressure are phenomena of different orders and should not be confused. Arterial disease is, in most of us, of much greater moment than the height of the arterial pressure. But its study represents a peculiar difficulty namely that

of determining its presence, extent and type prior to the occurrence of vascular catastrophe or the death of the patient' Secondly he holds that the arterial lesions in the benign phase of essential hypertension also occur in patients with lower blood pressures though perhaps less frequently and less severely Thirdly he states that the intensity of the hypertension is clearly a factor in the production of hypertensive heart failure. Fourthly the phenomena of the malignant phase are consequences of an extremely severe hypertension.

The relationship between hypertension and vascular disease is thus by no means clear Many authors believe that the level of the blood pressure is an index of the severity of the hypertensive disease, while others maintain that the vascular disease is the decisive factor Goldring (79) discusses this, and contends that 'we should be thinking in terms of vascular disease and severity of hypertensive disease, since vascular disease is the lethal agent. It is true that the vascular disease we are speaking of is more common in hypertensives than in normotensives. But its association does not necessarily prove that the vascular disease is caused by and is proportional to the blood pressure elevation

In the next place study of the literature shows that the frequency with which the different symptoms are reported differs greatly This applies to most of the symptoms, whether they are classified as cardiac, cerebral, renal, or psychoneurotic.

The most likely reason for this is that the series are selective. Firstly they are taken from highly dissimilar populations, some made up of private patients, others based upon hospital, or outpatient clientele. Next the material is selective with regard to age and blood pressure as various norms have been used.

The symptom frequency also depends upon the definitions with which the authors concerned comply next upon which symptoms the individual authors want to study and to which they attach most

weight. Finally the methods used are decisive.

The series representing different populations, different time periods, or different countries appear to agree as far as the frequency of some symptoms are concerned. As an example we may note that the frequency of dyspnoea is quite similar in the prognostic studies of Bechgaard (17) Janeway (105) and Mathisen (144) but not one of these authors has related the symptom to age. This symptom increases considerably with age, and studies that are not age-specific are of little value. The same objections apply to the great majority of studies of symptom frequency

Not only are the data on symptom frequency incomplete the same applies to the frequency of the different types of hypertension How common for instance, is secondary hypertension? We only know that it is rather uncommon and makes up from 5-10 % of all the cases when they are judged by the norms current up to now Pickering (177) thus states that it is a curious lapse that there are no figures known to the author to show how common the different forms of hypertension are in a population sample

In this introduction to the symptomatology and the clinical picture one can only emphasize the most important and more general points and with this in mind too much reference to the extensive literature will be avoided here. A more detailed survey and review of the literature of the cardiac signs and symptoms will be found in the following chapters.

The object of this survey presented in the two preceding chapters, has been to point out and comment on some of the problems of high blood pressure and the natural course of hypertension. Many expert committee reports on cardiovascular diseases and hypertension have been published in the last 10 years, emphasizing the urgent need of an epidemiological approach to the study of hypertension (see the WHO reports, 239-240) The Symposium

on Essential Hypertension in Boston 1931 (159) concluded, on the basis of an exhaustive review of the literature that although various studies leave no doubt that hypertension is a health problem of great magnitude which probably varies according to age, sex and race, they do not answer the question as to its exact extent or provide an accurate account of its distribution in any population.

### Summary

High blood pressure is to be looked upon as a symptom which can be assigned to various illnesses of greatly differing aetiology. A survey is given of the most important contributions to our understanding of hypertension from the days of Bright up to our time. A series of classifications of hypertension have been proposed over the last decades.

The criteria for normal and pathological blood pressure readings are reviewed. The blood pressure in several population studies from scattered parts of the world shows a continuous distribution and there is no natural dividing line between those with high blood pressure and those without.

There is such a pronounced increase in range of blood pressure with increasing age in both sexes that several authors have proposed new limits for the normal pressure and new limits for hypertension. However the life insurance statistics show figures that suggest that their criteria of a pathological blood pressure cannot be

disregarded. These criteria must be seen against the background of the selected series and particularly of the circumstances under which pressures are measured. Consequently these criteria cannot, without further ado, be applied to series in which the blood pressure is measured as a casual blood pressure.

The symptoms that accompany a raised blood pressure vary greatly. Because of their uncertain relationship to the raised pressure it is difficult to assess and to distinguish between the varieties of symptoms. Consequently in the literature one finds different proposals for the classification and grouping of symptoms. The relationship between hypertension and vascular disease is by no means clear. Many authors believe that the level of the blood pressure is an index of the severity of the hypertensive disease, while others maintain that the vascular disease is the decisive factor.

The frequency with which the different symptoms are reported differs greatly. This applies to most of the symptoms, whether they are classified as cardiac, cerebral, renal, or psychoneurotic. The most likely reason for this is that the series are selective, using various blood pressure norms and various definitions and methods of study.

Several expert committee reports on cardiovascular diseases and hypertension emphasize the urgent need for an epidemiological approach to the study of hypertension.

## CHAPTER III

# The basis of this epidemiological investigation

### The blood pressure in the population of Bergen

During the Second World War and in the years immediately following an increase in the morbidity and mortality of tuberculosis was registered in Norway and in most of the occupied countries. As a part of an efficient campaign against the tuberculous diseases two important Acts were passed. By 'The Act of December 12th 1947 respecting X-ray examination by mass radiography' and 'The Act of December 12th 1947 respecting tuberculin testing and inoculation against tuberculosis' the Director of Health was empowered to carry out the health measures in these Acts.

#### Collection of data

For the City of Bergen these health provisions were put into force in 1950 and permission was obtained to take the blood pressure of those who were required to present themselves for examination in accordance with these Acts. The investigations were performed in two stages, the first during the period January to June 1950 (Group I) and the second during the period January to May 1951 (Group II).

Of the total population of Bergen on January 1st 1950 there were 88,339 persons over 14 years of age. Of these some were exempt from attendance, viz. those medically certified as unfit to attend, those who had already been mass X-rayed in other places, those who were already on

the Tuberculosis Register and students who were temporarily absent for studies in other cities or countries.

The city was divided into districts and sub-districts, and attendance was arranged according to streets. The examinations were carried out in the local schools, and there were separate days for men and women with suitable opening hours so that everybody could choose the most convenient time.

At the examination each person was registered by sex, age, occupation, and address, and was given an identification number. No medical details of earlier diseases were asked for either of tuberculosis or of possible cardiovascular disease.

The number of people attending the mass radiography is shown in Table 3.1

Table 3.1 *The attendance for mass radiography and blood pressure measurement of the population of Bergen 1950 and 1951*

|  |        |
|--|--------|
| Subject to compulsory mass radiography on 1 January 1950   | 88,339 |
| Exempt from attendance at the time of investigation (January to June 1950 and January to May 1951) |        |
| ( ) Dead   |        |
| (b) Left Bergen permanently  |        |
| ( ) Already mass X-rayed elsewhere   |        |
| (d) Students temporarily absent  |        |
| ( ) Already on the Tuberculosis Register   |        |
| (f) Certified medically unfit to attend  |        |
| Total categories a-f   | 7,868  |
| Failed to attend   | 10,016 |
| Mass X-rayed   | 70,455 |
| Blood pressure measured  | 67,976 |

Of the total number required to present themselves for examination, 86.7 per cent attended. Of those who presented themselves for the compulsory mass radiography a total of 67 976 persons, or 96.3 per cent, were examined with regard to blood pressure. For various reasons not all of them could be examined in this respect also — they were too busy could not wait and so forth.

#### *The method of measurement*

In the examination room small separate cubicles were provided where the blood pressure readings could be taken in peace and privacy.

Blood pressures were measured by nurses who had been specially trained for this purpose in the Department of Medicine University Clinic of Bergen. They did their work very conscientiously and were particularly careful to maintain an atmosphere of calm and quiet around them. To avoid queues and to ensure that the readings would be made as smoothly and quietly as possible, there were always enough nurses to have one in reserve. They alternated so as to a void fatigue.

The blood pressure was read according to the recommendations of the Committee for the standardization of blood pressure readings of the American Heart Association and the Committee for the standardization of blood pressure readings of the Cardiac Society of Great Britain and Ireland (219).

The blood pressure was first measured by the palpatory method and then measured once or twice by the auscultatory method. The diastolic pressure was read at phase V. In cases where this phase was not distinct, the diastolic pressure was taken at phase IV (muffling of the sounds). Of various readings in the same person, the lowest pressure was recorded. The pressure was read to the nearest 5 mm (see p. 67).

Mercury manometers with a 15 cm wide cuff were used. The readings were

taken in a sitting position with the person sitting on a chair with the arm placed horizontally on a table.

During the second part of these investigations (Group II January to May 1951) height and weight were also registered.

#### *The results of the measurements*

Further details of the results of the blood pressure measurements of the population of the city of Bergen will be found in the publication of Bøe, Humerfelt & Wedervang (30). This investigation comprises a thorough analysis of the blood pressure according to sex and age, height and weight patterns in the population, the influence of height, weight, and age on the blood pressure including the influence of excess mortality on the blood pressure pattern and a two-dimensional description of the blood pressure.

Details of importance in connection with this study will be commented upon in the following chapters.

During the collection of the data and the preliminary work during 1950, it was evident that the material could be of value for a closer study of the epidemiology of high blood pressure.

This study was then planned in further detail during the autumn of 1950 and contemporary to the blood pressure measurement of 1951 and the work is based upon that part of the population of Bergen which was examined in 1950 (group I) including a total of 44 182 individuals over 15 years of age.

#### **The population of the City of Bergen in 1950 and their attendance for mass radiography and blood pressure recording in this year**

Bergen is divided into 10 parishes. The northern and central districts of the city make up the first 8 parishes (group I) the



population on which this work is based (see Table 3.3). The southern part consists of the 2 last parishes (group II) which are not included in this study.

In order to judge how far the material obtained from the mass radiography and blood pressure measurements is representative of the whole population, one must first know the size of the population and its distribution between the different age groups and the sexes at the time of the investigation (January to June 1950). Next one must find out the attendance rate within the age groups and the sexes.

We have no exact figures for the size of the population in the separate parts of the city in the year 1950. A census was taken on 15.11.1948 and on 15.11.1952.

The total resident population of Bergen showed very little change in the 4-year period from 1948-52, though the number of people was somewhat less in 1950 than in the years before and after as is shown in Table 3.2.

Table 3.2. Resident population according to estimated figures

| Year | Resident population | Mean population | Increment |              |
|------|---------------------|-----------------|-----------|--------------|
|      |                     |                 | Absolute  | Per thousand |
| 1948 | 114 196             | 113,903         | 586       | 5.16         |
| 1949 | 114 194             | 114 193         | — 2       | — 0.02       |
| 1950 | 112,801             | 113,498         | — 1,393   | — 12.20      |
| 1951 | 113,289             | 113 045         | 488       | 4.33         |
| 1952 | 113 489             | 113,389         | 200       | 1.77         |

All censuses include details of age and sex within the parishes. On comparing the census of 1948 to that of 1952 one finds a regular change in the population size and distribution. The total number of the residents dropped by about 3,400 in group I in the four year period, however group II showed a corresponding increase in population over the same time (see Table 3.3).

This represents a movement of the popu-

Table 3.3. Resident population distributed in parishes

|   | Parishes   | Number of inhabitants |         | Per cent distribution |        |
|---|------------|-----------------------|---------|-----------------------|--------|
|   |            | 1948                  | 1952    | 1948                  | 1952   |
| Group I   | Domkirken  | 13 449                | 12,786  | 12.00                 | 11.27  |
|   | Johannes   | 13,477                | 13,049  | 12.02                 | 11.50  |
|   | St. Jacob  | 2,293                 | 2,107   | 2.05                  | 1.86   |
|   | Marin      | 4,271                 | 4,001   | 3.81                  | 3.53   |
|   | Sand Breen | 13,733                | 13,494  | 14.94                 | 13.66  |
|   | St. Olav   | 5,700                 | 5,313   | 5.09                  | 4.68   |
|   | Korskirken | 7 702                 | 7,023   | 6.87                  | 6.19   |
| Subtotal  | Nidariken  | 8,634                 | 8,066   | 7.79                  | 7.11   |
|   |            | 71,261                | 67,839  | 63.53                 | 59.80  |
| Group II  | Årstad     | 31 748                | 35,604  | 28.33                 | 31.45  |
|   | St. Markus | 7 418                 | 7,817   | 6.62                  | 6.88   |
| Subtotal  |            | 39 166                | 43,501  | 34.95                 | 38.33  |
| Persons of unknown fixed place of residence in Bergen |            | 1,650                 | 2 122   | 1.47                  | 1.87   |
| Total   |            | 112,077               | 113,462 | 100.00                | 100.00 |

lation from the northern and central parts of the city to the southern, but the total resident population of Bergen has shown very little change.

When dividing the censuses into age and sex groups in the same four-year period (grouped 5 yearly from the age of 15 to 29 years, and 10 yearly from 30 years and upwards) one finds a systematic change in the numbers obtained. The younger age groups — up to 40-49 years — show lower values in 1952 than in 1948. In the 50-year group and upwards the figures show slight, but systematic increase. This is true for both sexes.

Fig 3.1 shows this population change in group I graphically.

This migration of the population is due for the most part to the younger age groups moving to the southern parts of the city. Within this four year period there was a considerable amount of residential building in Bergen, and this has taken place mainly on the south side of the city. The numbers in group II as shown in Table 3.3

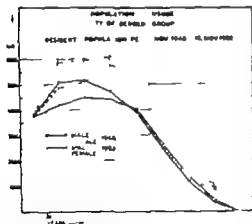


Fig 3.1 The diagram shows the population change in group I. The population in the younger age groups — up to 50 years of age — is clearly lower in 1952 than it was in 1948. From 50 years of age there is a regular but slight increase from 1948 to 1952. These changes appear to be almost the same for both sexes.

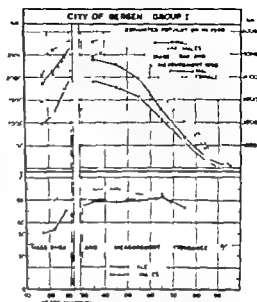


Fig 3.2. The diagram shows the attendance of the population at the mass radiography and blood pressure measurement 1950 divided into sex and age groups.

are found to have increased correspondingly.

To estimate the population in the year 1950 when the mass radiography and the blood pressure measurements were taken one must interpolate the figures from the censuses of 15.11.1948 and 15.11.1952. (The method of calculation was checked by the City of Bergen Bureau of Statistics, Director O. Støv). This interpolation is relatively simple as the mass radiography was carried out midway between the censuses. Thus the estimated population will be the average of these figures (Table 3.4).

The attendance of the population at the mass radiography and blood pressure measurement in 1950 divided into age and sex groups, is shown in Table 3.5. The percentage attendance has been calculated from the estimated population.

A graphical representation of this is seen in Fig 3.2., drawn for men and women separately.

*Table 3.4 Population censuses  
Resident population of Group I on 15/II-48 and 15/II-52 compared with estimated population 1950. Age  
and sex distribution*

|         | Years                           | 15-19 | 20-24 | 25-29 | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70  | Sub-<br>total |
|---------|---------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|---------------|
| Males   | 1948                            | 1,906 | 2,209 | 2,873 | 5,140 | 4,685 | 3,971 | 2,486 | 1,954 | 23,096        |
|         | 1952                            | 1,838 | 2,097 | 2,111 | 4,525 | 4,442 | 4,007 | 2,707 | 1,882 | 23,609        |
|         | Difference                      | - 88  | - 112 | - 764 | - 615 | - 43  | + 86  | + 221 | + 28  | - 1,487       |
|         | Estimated<br>population<br>1950 | 1,882 | 2,153 | 2,493 | 4,832 | 4,563 | 3,963 | 2,596 | 1,868 | 23,949        |
| Females | 1948                            | 2,124 | 2,643 | 3,100 | 5,951 | 6,088 | 5,190 | 3,703 | 3,379 | 32,299        |
|         | 1952                            | 1,971 | 2,463 | 2,390 | 5,119 | 5,752 | 5,507 | 3,936 | 3,557 | 30,719        |
|         | Difference                      | - 153 | - 299 | - 710 | - 832 | - 336 | + 31  | + 253 | + 178 | - 1,580       |
|         | Estimated<br>population<br>1950 | 2,048 | 2,614 | 2,746 | 5,535 | 5,920 | 5,348 | 3,829 | 3,467 | 31,507        |

*Total Males and Females*

|            |         |
|------------|---------|
| 1948       | 57,395  |
| 1952       | 54,328  |
| Difference | - 3,067 |
| 1950       | 33,456  |

The attendance rate for mass radio-graphy by percentage varied in the different age and sex groups. There was a poor attendance for men and women up to the age of 25 years, and particularly low for young men aged 15-19 years and 20-24 years, 51 and 53 respectively. In the succeeding age groups the attendance was considerably better and regularly higher for women. The best attendance was for women in the 40-49 year group being 90. In the highest age group (over 70 years) there was again a drop in the percentage in both sexes, but this was least for the women. The average attendance of the population in this area was 80 somewhat lower for the men (75) than for the women 83.

### Discussion

These data of the attendance rates are somewhat different from those given by

Böe, Humerfelt & Wedervang for the Bergen series (see their Table 8, page 53). The calculations were then made for the series as a whole (groups I and II combined) and show that the total percentage attendance was 70 for men and 82.4 for women. Table 3.5 of this monograph shows the attendance of the population in group I only. By comparing the different data it can be seen that the attendance was better in group I than in group II.

Any evaluation of the degree to which the series is representative of the adult population of the city of Bergen must be based on the attendance rate. Because of the poor attendance the series cannot be considered representative for men from 15-29 years and for women from 15-19 years or for the over 70-year age groups in both sexes. One sees that apart from these age groups the attendance rate for men from 30-69 years of age averaged

Table 3.5. Attendance for mass radiography and blood pressure measurement 1950 Group 1 Percentage attendance according to estimated population 1950

| Years                   | 15-19 | 20-24 | 25-29 | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70  | Subtotal |
|-------------------------|-------|-------|-------|-------|-------|-------|-------|-------|----------|
| Males                   | 962   | 1 148 | 1 746 | 3,800 | 3,566 | 3 156 | 2 149 | 1,374 | 17,901   |
| Per cent                | 51    | 53    | 70    | 79    | 8     | 80    | 83    | 74    | 75       |
| Females                 | 1 425 | 1,057 | 2 427 | 4,901 | 5,318 | 4,579 | 3,279 | 302   | 26,281   |
| Per cent                | 70    | 79    | 83    | 87    | 90    | 86    | 8     | 64    | 83       |
| Total Males and Females |       |       |       |       |       |       |       |       | 44 182   |
| Per cent                |       |       |       |       |       |       |       |       | 80       |

80 and for women 86 that is a lapse rate of 20% and 14% respectively.

Even though this must be considered a relatively good attendance for a mass investigation of this type one must make reservations with regard to the representativeness of the series.

When the work was planned it was realized that a certain number of lapses could not be avoided if the investigation was to be based on the whole of the adult population. But due to the fact that the mass-radiography was compulsory it was hoped that the attendance would be satisfactory at any rate for the young and middle aged.

In many ways a better sample of the population will be obtained if one does not attempt to investigate all those concerned. From a statistical point of view it is evident that the figures obtained from a cross-section of the population are more reliable than an investigation based on the whole population where the lapse rate throws some doubt on its representativeness. Bradford Hill (97) thus says: 'I would therefore myself infinitely sooner have, say a one in four sample of the population, of a size thereby which enabled me to pursue relentlessly and complete the records for all, or nearly all the persons in it, than have to interpret figures derived from a survey of the "whole" population from which finally a quarter was missing'. In the same connection R. Doll (32) writes: 'It is perhaps generally reasonable to allow a lapse rate of up to 5 per cent,

but a lower one should always be aimed at and it must be realized that anything appreciably higher may materially bias the results. If a series fulfilling these criteria of true representativeness were to be obtained the blood pressure measurements would have to be taken in the homes or at work.

It is regrettable that the lapse rate in the primary series is so great that the series must be deemed selective. In addition this selection varies in the different age groups and this again can lead to fallacious inferences. Malmgren (137) in his review of *The Blood Pressure in a Population* has touched on this problem of selection and refers to Berkson (24). In that statistical study (of the association between smoking and lung cancer) it is pointed out that selection can produce spurious correlation in prospective studies. Berkson claims that, 'More broadly considered, wherever it is found that selection is operating, it is gratuitous to assume that selection does not affect differentially different strata of the population sampled, and therefore one must be prepared to find differences between corresponding strata in the sample, even if there are none in the original population.

The reason why the young men's attendance is lowest is may be that this age group comes under regular health inspection at school, during training and military service, when mass radiography is included as a compulsory and routine investigation. It is therefore reasonable

that this age group should not show the same attendance as the other age groups.

The reason why men as a whole show a poorer attendance than women can in part be explained by the work of the industrial medical officers and factory doctors, which is carried out in most of the large and middle-sized businesses in Bergen. Here the workers and office staff undergo regular health examinations, including mass radiography. It is possible that this may account for the men concerned.

The drop in attendance in the oldest age group (over 70 years) is naturally explained by failing health and decrease in mobility. However it must be remembered that many of these people live in old age, convalescent, and nursing homes. Here they undergo routine health examinations, and so the same grounds for non-attendance can also exist for this age group.

### Summary

A short description is given of the mass radiography and blood pressure investigation of the population of Bergen in 1950-51. Further details will be found in the publication by Bøe, Humerfelt & Wedervang (34).

The blood pressure was first measured by the palpatory method and then measured once or twice by the auscultation method. The diastolic pressure was read at phase V. In cases where this phase was not distinct, the diastolic pressure was taken at phase IV.

The present study was planned during the autumn of 1950 and the work is based upon the part of the Bergen population that was examined in 1950 (group I), including a total of 44 182 individuals of 15 years of age.

An estimation of the representativeness of the primary series (group I) is given. The attendance, calculated from the estimated population in 1950, averaged 80%, somewhat lower for the men (75%) than for the women (83%). There was a poor attendance for men and women up to the age of 25 years, particularly for young men. The best attendance was for women in the 40-49 age group, being 90%. In the highest age group there was again a drop.

One must make reservations with regard to the representativeness of the series. The lapse rate is so great that the series must be deemed selective. The selectivity varies in the different age groups and it again can lead to fallacious inference.

## CHAPTER IV

### The aims of the investigation and plan of study

This work is an epidemiological study. In contrast to clinical medicine the unit in epidemiological investigations is the *group* and not the individual. Morris (154) gives the following main characteristics: 'The clinician deals with cases. The epidemiologist deals with cases in their population. He may start with a population and seek out the cases in it, or start with the cases and refer them back to a population, or what can be taken to represent a population.'

This method is of special interest in increasing our understanding of cardiovascular disease. Thus there is almost universal agreement, according to Dawber & co-workers (47) that of the epidemiology of hypertensive or arteriosclerotic cardiovascular disease almost nothing is known, although these two account for the great bulk of deaths from cardiovascular disease. The scanty epidemiological knowledge of these diseases which does exist is based either on the study of mortality statistics, which in the investigation of long term diseases are often not very revealing, or on clinical studies, which have the disadvantage from the epidemiologist's point of view of being based on the study of those who already have the disease. Clearly what is required is the epidemiological study of these diseases based on populations of normal composition, including both the sick and the well as they are found in the community.

It has been pointed out in the preceding chapter that there are several fundamental gaps in our knowledge of the real meaning

of a raised blood pressure. Thus we know nothing definite of the degree to which a raised blood pressure affects or damages the well-being of an individual. In other words, how sick are these individuals? How are their symptoms manifested? Studies of the literature show that all our knowledge of the injurious effect of a raised blood pressure is based on series that are to a greater or lesser extent selective.

The Bergen series comprises all age groups over 15 years old of both sexes. It is to be noted that this primary series shows all levels of blood pressure — taken as casual readings. An attempt has been made (see p. 31) to show to what extent the series is representative of the population of the city of Bergen, and it is concluded that the series is not really representative of all age groups.

However even though there are definite gaps in the material as a result of the poor attendance in certain age groups, it is, as far as we can see, one of the few series published to date which comes nearest to embracing the whole population of a city.

It is therefore thought that it could be of value to use this series to answer some of the above questions.

*The aim of this work is to investigate some of the problems of the epidemiology of high blood pressure and the hypertensive diseases.*

Representative groups of individuals, belonging to both sexes and including all age groups and different blood pressure levels will be selected at random from the primary series.

that this age group should not show the same attendance as the other age groups.

The reason why men as a whole show a poorer attendance than women can in part be explained by the work of the industrial medical officers and factory doctors, which is carried out in most of the large and middle-sized businesses in Bergen. Here the workers and office staff undergo regular health examinations, including mass radiography. It is possible that this may account for the men concerned.

The drop in attendance in the oldest age group (over 70 years) is naturally explained by failing health and decrease in mobility. However it must be remembered that many of these people live in old age, convalescent, and nursing homes. Here they undergo routine health examinations, and so the same grounds for non-attendance can also exist for this age group.

### Summary

A short description is given of the mass radiography and blood pressure investigation of the population of Bergen in 1950-51. Further details will be found in the publication by Bøe, Humerfelt & Wedervang (34).

The blood pressure was first measured by the palpatory method and then measured once or twice by the auscultatory method. The diastolic pressure was taken at phase V. In cases where this was not distinct, the diastolic pressure was taken at phase IV.

The present study was planned in the autumn of 1950 and the work is upon the part of the Bergen population that was examined in 1950 (group I), including a total of 44 182 individuals 15 years of age.

An estimation of the representativeness of the primary series (group I) is given. The attendance, calculated from the estimated population in 1950 averaged somewhat lower for the men (75 %) than for the women (83 %). There was a lower attendance for men and women up to the age of 25 years, particularly for men. The best attendance was for men in the 40-49 age group, being 90%. In the highest age group there was again a lower attendance.

One must make reservations with regard to the representativeness of the series. The lapse rate is so great that the series must be deemed selective. The selection varies in the different age groups and again can lead to fallacious infer-

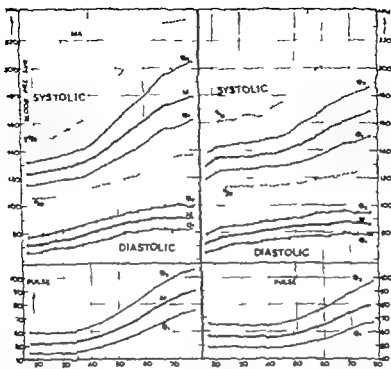


Fig. 4.1 The Bergen Series, Group 1. The blood pressure distribution according to sex and age. Half the population has higher and half the population has lower pressure than the median, 1/4 of the population has lower than the lower quartile and 1/4 has higher pressure than the upper quartile.

consider to be a normal or a pathological blood pressure within the different age groups in the two sexes.

Further with the help of this series drawn from a population group it may be possible to answer one of the problems put forward by Pickering (176) — namely whether the signs and symptoms due to the raised blood pressure are qualitatively different from those with normal blood pressure or whether the difference is only purely quantitative.

The other main task, *the longitudinal study* will be touched upon very shortly. This grouped series will be well suited to a long-term and prognostic study of the type of the Framingham investigation (47) but on a smaller scale.

This part of the survey will not be explored further at this point. Because of this a closer evaluation of the prognostic studies to date will not be given here except in so far as it touches upon the present work.

#### Selection of the miniature series (subsample)

The primary series of group 1 comprises a total of 44 152 individuals, 17,901 men and 26,251 women. The blood pressure distribution in the different age groups and sexes is shown in Tables 4.1 and 4.2 and is illustrated in Fig. 4.1.

The selection of the grouped series, which will hereafter be referred to as the



*Table 4.1 Frequency distribution of systolic blood pressure by age*  
Males Group 1

| Systolic | Age   |       |       |       |       |       |       |       |       |       |       |       |     | Total  |
|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-----|--------|
|          | 15-19 | 20-4  | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 | 75- |        |
| Under 90 |       |       |       |       |       |       |       |       |       |       | 1     |       |     | 1      |
| 90       |       |       |       |       |       |       | 2     |       |       |       |       |       |     | 9      |
| 95       | 3     | 4     |       |       |       | 1     |       |       |       |       |       |       |     | 5      |
| 100      | 16    | 8     | 6     | 7     | 8     | 9     | 1     | 1     | 7     |       |       | 1     | 3   | 78     |
| 105      | 17    | 8     | 15    | 17    | 18    | 8     | 9     | 7     | 3     |       |       | 1     | 1   | 103    |
| 110      | 83    | 43    | 81    | 66    | 53    | 59    | 47    | 54    | 23    | 18    | 9     | 11    | 6   | 537    |
| 115      | 52    | 27    | 52    | 58    | 65    | 51    | 40    | 44    | 23    | 10    |       |       | 3   | 432    |
| 120      | 20    | 148   | 210   | 113   | 229   | 178   | 165   | 119   | 78    | 53    | 31    | 24    | 1   | 1,667  |
| 125      | 57    | 62    | 85    | 74    | 92    | 83    | 82    | 44    | 33    | 11    | 9     | 7     | 5   | 644    |
| 130      | 218   | 965   | 403   | 406   | 390   | 328   | 74    | 228   | 180   | 114   | 70    | 37    | 19  | 2,932  |
| 135      | 34    | 59    | 81    | 119   | 95    | 96    | 69    | 58    | 56    | 4     | 11    | 13    | 10  | 43     |
| 140      | 156   | 969   | 391   | 415   | 404   | 417   | 331   | 303   | 202   | 14    | 85    | 71    | 62  | 3,448  |
| 145      | 16    | 33    | 44    | 54    | 64    | 61    | 60    | 59    | 46    | 31    | 18    | 19    | 8   | 311    |
| 150      | 63    | 116   | 71    | 233   | 237   | 226   | 242   | 251   | 203   | 154   | 115   | 84    | 5   | 2,166  |
| 155      | 6     | 8     | 15    | 19    | 77    | 58    | 38    | 28    | 27    | 70    | 18    | 16    | 11  | 271    |
| 160      | 22    | 64    | 92    | 110   | 137   | 146   | 148   | 183   | 190   | 197   | 119   | 91    | 94  | 1,593  |
| 165      | 3     | 2     | 6     | 5     | 6     | 13    | 1     | 23    | 19    | 23    | 23    | 12    | 15  | 162    |
| 170      | 6     | 22    | 58    | 58    | 55    | 64    | 88    | 142   | 132   | 163   | 116   | 99    | 65  | 1,050  |
| 175      | 1     |       |       | 3     | 3     | 3     | 10    | 14    | 15    | 11    | 14    | 15    | 11  | 98     |
| 180      | 1     | 5     | 11    | 17    | 1     | 36    | 4     | 79    | 81    | 96    | 81    | 78    | 80  | 614    |
| 185      |       |       |       |       |       | 2     | 3     | 3     | 2     | 7     | 9     | 4     | 10  | 44     |
| 190      |       | 4     | 3     | 7     | 6     | 12    | 18    | 35    | 39    | 63    | 49    | 52    | 46  | 334    |
| 195      |       |       |       |       |       | 1     | 1     | 2     | 9     | 5     | 4     | 8     | 2   | 55     |
| 200      |       | 1     | 1     | 4     | 1     | 11    | 18    | 22    | 32    | 52    | 23    | 33    | 34  | 232    |
| 205      |       |       |       |       |       |       |       |       |       | 2     |       | 2     | 1   | 5      |
| 210      |       |       |       |       | 4     | 5     | 6     | 15    | 23    | 14    | 25    | 40    | 33  | 167    |
| 215      |       |       |       |       |       |       | 1     |       |       | 1     |       | 1     |     | 3      |
| 220      |       |       |       |       |       |       | 4     | 7     | 11    | 19    | 23    | 14    | 13  | 93     |
| 225      |       |       |       |       |       |       |       |       |       | 1     | 1     |       | 1   | 3      |
| 230      |       |       |       |       | 1     | 1     |       | 3     | 8     | 9     | 14    | 7     | 10  | 34     |
| 235      |       |       |       |       |       | 1     |       |       |       | 1     | 1     |       |     | 3      |
| 240      |       |       |       |       |       | 1     | 1     | 1     | 5     | 5     | 6     | 3     | 7   | 29     |
| 245      |       |       |       |       |       |       |       |       |       |       |       |       |     |        |
| 250      |       |       |       |       |       |       | 1     |       | 3     | 5     | 4     | 5     | 5   | 23     |
| 255      |       |       |       |       |       |       |       |       |       |       |       |       |     |        |
| 260      |       |       |       |       |       |       |       | 1     |       | 1     | 3     | 1     |     | 6      |
| 265      |       |       |       |       |       |       |       |       |       |       | 1     |       |     | 1      |
| 270      |       |       |       |       |       |       |       |       |       | 3     | 5     | 1     | 2   | 11     |
| 275      |       |       |       |       |       |       |       |       |       |       |       |       |     |        |
| 280      |       |       |       |       |       |       |       |       |       |       | 1     |       |     | 1      |
| 285      |       |       |       |       |       |       |       |       |       |       |       |       |     |        |
| 290      |       |       |       |       |       |       |       |       |       |       |       |       |     |        |
| 295      |       |       |       |       |       |       |       |       |       |       |       |       |     |        |
| 300      |       |       |       |       |       |       |       |       |       |       |       | 1     |     | 1      |
| Total    | 962   | 1,148 | 1,746 | 1,889 | 1,911 | 1,833 | 1,15  | 1,712 | 1,444 | 1,555 | 894   | 751   | 623 | 17,901 |

Table 4-1 Frequency distribution of systolic blood pressure by  
Females Group 1

| Systolic<br>Pressure | Age:  |       |       |       |       |       |       |       |       |       |       |       |       | Total  |
|----------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|
|                      | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 | 75+   |        |
| 90                   |       |       |       | 1     |       |       |       |       |       |       |       |       |       | 1      |
| 95                   | 6     | 5     | 5     | 2     | 4     | 2     |       | 1     |       |       |       |       |       | 23     |
| 100                  | 7     | 2     | 5     | 5     |       | 2     |       |       |       |       |       |       |       | 21     |
| 105                  | 49    | 71    | 41    | 27    | 30    | 21    | 9     | 4     | 6     | 5     | 1     |       |       | 264    |
| 110                  | 26    | 50    | 31    | 1     | 29    | 16    | 11    | 4     |       |       | 1     |       |       | 169    |
| 115                  | 208   | 273   | 269   | 216   | 196   | 115   | 63    | 34    | 21    | 12    | 5     | 3     | 3     | 1,418  |
| 120                  | 62    | 92    | 114   | 104   | 84    | 76    | 49    | 27    | 7     | 7     | 3     | 1     | 2     | 628    |
| 125                  | 408   | 529   | 572   | 497   | 434   | 355   | 251   | 132   | 73    | 30    | 15    | 15    | 9     | 3,520  |
| 130                  | 52    | 94    | 129   | 93    | 97    | 93    | 53    | 44    | 21    | 17    | 5     | 1     | 2     | 703    |
| 135                  | 532   | 507   | 576   | 571   | 520   | 505   | 570   | 274   | 163   | 97    | 44    | 31    | 27    | 4,017  |
| 140                  | 58    | 45    | 76    | 77    | 94    | 109   | 85    | 62    | 51    | 21    | 17    | 13    | 11    | 693    |
| 145                  | 174   | 288   | 395   | 445   | 525   | 574   | 506   | 385   | 244   | 161   | 101   | 62    | 58    | 3,898  |
| 150                  | 10    | 15    | 22    | 30    | 48    | 61    | 88    | 73    | 55    | 32    | 28    | 17    | 6     | 483    |
| 155                  | 43    | 70    | 133   | 157   | 236   | 325   | 415   | 367   | 273   | 202   | 132   | 111   | 67    | 2,531  |
| 160                  | 1     | 8     | 9     | 14    | 20    | 30    | 54    | 47    | 43    | 33    | 27    | 24    | 12    | 322    |
| 165                  | 8     | 21    | 40    | 50    | 113   | 178   | 266   | 329   | 299   | 247   | 189   | 121   | 127   | 1,988  |
| 170                  |       | 1     | 2     | 19    | 7     | 11    | 27    | 35    | 34    | 37    | 23    | 20    | 22    | 238    |
| 175                  |       | 5     | 6     | 24    | 63    | 98    | 176   | 244   | 254   | 240   | 196   | 157   | 158   | 1,621  |
| 180                  | 1     | 1     | 1     | 6     | 19    | 45    | 98    | 145   | 181   | 168   | 168   | 124   | 142   | 1,098  |
| 185                  |       |       |       |       | 1     | 2     | 4     | 12    | 14    | 19    | 12    | 14    | 12    | 90     |
| 190                  |       |       |       | 5     | 6     | 21    | 39    | 76    | 127   | 125   | 123   | 93    | 101   | 716    |
| 195                  |       |       |       |       | 1     | 1     | 1     | 4     | 10    | 9     | 8     | 10    | 11    | 54     |
| 200                  |       |       |       | 1     | 2     | 8     | 32    | 62    | 69    | 98    | 117   | 91    | 112   | 592    |
| 205                  |       |       |       |       | 1     |       |       |       | 3     | 3     | 5     | 3     | 1     | 16     |
| 210                  |       |       |       |       | 2     | 6     | 21    | 40    | 49    | 69    | 98    | 87    | 87    | 459    |
| 215                  |       |       |       |       |       | 1     | 1     | 2     | 3     | 3     | 2     | 5     | 4     | 20     |
| 220                  |       |       |       |       | 1     | 1     | 9     | 27    | 26    | 47    | 47    | 57    | 47    | 262    |
| 225                  |       |       |       |       |       |       |       | 3     |       | 11    | 1     | 4     | 1     | 15     |
| 230                  |       |       |       |       |       | 1     | 8     | 10    | 20    | 20    | 31    | 36    | 41    | 167    |
| 235                  |       |       |       |       |       |       |       |       |       | 2     | 1     | 2     | 1     | 6      |
| 240                  |       |       |       |       | 1     | 1     | 1     | 9     | 10    | 14    | 27    | 32    | 26    | 121    |
| 245                  |       |       |       |       |       |       | 1     |       | 5     | 2     |       |       | 2     | 8      |
| 250                  |       |       |       |       |       |       |       | 3     | 2     | 15    | 10    | 10    | 15    | 55     |
| 255                  |       |       |       |       |       |       |       | 1     |       |       | 1     |       |       | 2      |
| 260                  |       |       |       |       |       | 1     | 2     | 3     | 2     | 7     | 7     | 13    | 9     | 43     |
| 265                  |       |       |       |       | 1     |       |       |       |       |       | 1     |       |       | 2      |
| 270                  |       |       |       |       |       |       |       | 1     | 2     | 5     | 11    | 1     | 6     | 26     |
| 275                  |       |       |       |       |       |       |       |       |       |       | 1     |       |       | 1      |
| 280                  |       |       |       |       |       |       |       |       |       | 1     | 2     | 3     |       | 6      |
| 285                  |       |       |       |       |       |       |       |       |       |       | 1     |       |       | 1      |
| 290                  |       |       |       |       |       |       |       |       |       | 2     | 2     | 1     | 1     | 6      |
| 295                  |       |       |       |       |       |       |       |       |       |       |       |       | 1     | 1      |
| 300                  |       |       |       |       |       |       |       |       |       |       |       |       |       | 1      |
| Total                | 1,425 | 2,057 | 2,427 | 2,363 | 2,538 | 2,666 | 2,652 | 2,487 | 2,083 | 1,789 | 1,490 | 1,185 | 1,117 | 26,281 |

Table 4.2. Frequency distribution of diastolic blood pressure by age

| Dia-<br>stolic  | Age   |       |       |       |       |       |       |       |       |       |       |       |       | Total  |
|-----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|
|                 | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 | 75-   |        |
| Males Group 1   |       |       |       |       |       |       |       |       |       |       |       |       |       |        |
| Under           |       |       |       |       |       |       |       |       |       |       |       |       |       |        |
| 40              | 3     |       |       |       | 4     | 1     |       |       |       |       | 1     |       |       | 9      |
| 40              | 6     |       |       | 3     | 1     | 2     |       |       |       |       | 1     |       |       | 21     |
| 45              | 5     | 3     | 2     | 1     | 1     |       |       |       | 1     | 1     | 1     |       | 2     | 12     |
| 50              | 30    | 14    | 16    | 10    | 3     | 4     | 2     | 3     | 4     | 2     | 1     | 4     | 3     | 96     |
| 55              | 17    | 16    | 11    | 10    | 3     |       | 3     |       | 1     | 2     | 1     | 3     |       | 67     |
| 60              | 158   | 111   | 112   | 97    | 90    | 53    | 46    | 34    | 36    | 25    | 16    | 27    | 21    | 826    |
| 65              | 46    | 51    | 71    | 46    | 53    | 44    | 35    | 26    | 18    | 24    | 12    | 10    | 8     | 444    |
| 70              | 330   | 291   | 421   | 397   | 364   | 297   | 287   | 201   | 162   | 138   | 84    | 76    | 69    | 4,116  |
| 75              | 44    | 65    | 91    | 111   | 119   | 89    | 72    | 76    | 53    | 38    | 30    | 23    | 12    | 873    |
| 80              | 209   | 335   | 568   | 635   | 590   | 577   | 470   | 467   | 395   | 321   | 200   | 143   | 134   | 5,044  |
| 85              | 16    | 31    | 46    | 76    | 76    | 84    | 72    | 60    | 62    | 43    | 46    | 31    | 14    | 659    |
| 90              | 84    | 194   | 336   | 383   | 441   | 509   | 464   | 483   | 374   | 323   | 242   | 222   | 176   | 4,253  |
| 95              | 8     | 16    | 23    | 33    | 45    | 60    | 62    | 59    | 55    | 41    | 25    | 27    | 20    | 472    |
| 100             | 6     | 18    | 34    | 67    | 92    | 93    | 125   | 180   | 154   | 161   | 116   | 103   | 78    | 1,227  |
| 105             |       | 1     |       | 6     | 15    | 8     | 13    | 22    | 20    | 21    | 14    | 13    | 9     | 146    |
| 110             |       |       | 10    | 10    | 9     | 30    | 44    | 68    | 69    | 63    | 55    | 48    | 36    | 444    |
| 115             |       |       | 1     | 1     | 1     | 5     | 5     | 2     | 6     | 8     | 6     | 1     | 4     | 30     |
| 120             |       |       | 1     | 2     | 3     | 11    | 10    | 18    | 18    | 25    | 20    | 13    | 9     | 130    |
| 125             |       |       |       |       |       | 1     |       | 3     | 1     |       | 1     | 1     | 2     | 9      |
| 130             |       |       |       |       |       | 4     | 3     | 3     | 10    | 12    | 10    | 3     | 4     | 49     |
| 135             |       |       |       |       |       | 1     |       | 1     | 1     |       |       |       |       | 3      |
| 140             |       |       |       |       |       |       | 1     | 3     | 6     | 4     | 9     | 1     | 2     | 26     |
| Over 140        |       |       |       |       | 1     |       |       | 1     |       | 1     | 3     |       |       | 6      |
| Total           | 962   | 1,148 | 1,746 | 1,689 | 1,911 | 1,853 | 1,713 | 1,712 | 1,444 | 1,255 | 894   | 731   | 623   | 17,901 |
| Females Group 1 |       |       |       |       |       |       |       |       |       |       |       |       |       |        |
| Under           |       |       |       |       |       |       |       |       |       |       |       |       |       |        |
| 40              | 1     |       | 1     | 1     |       | 1     |       |       | 1     | 1     | 1     | 1     |       | 10     |
| 40              | 4     | 3     |       | 4     | 1     |       | 1     |       | 3     | 1     | 1     | 4     |       | 21     |
| 45              | 3     | 3     | 1     | 2     |       | 2     |       |       |       |       |       |       |       | 13     |
| 50              | 31    | 43    | 14    | 9     | 2     | 6     | 1     | 2     | 2     | 1     | 3     | 1     | 3     | 123    |
| 55              | 16    | 17    | 12    | 8     | 8     | 2     | 3     | 1     | 1     | 1     | 1     |       | 3     | 72     |
| 60              | 221   | 281   | 239   | 183   | 132   | 105   | 79    | 40    | 36    | 31    | 25    | 20    | 15    | 1,417  |
| 65              | 77    | 93    | 95    | 69    | 57    | 61    | 34    | 30    | 21    | 13    | 9     | 10    | 7     | 576    |
| 70              | 362   | 786   | 835   | 767   | 687   | 525   | 410   | 242   | 198   | 108   | 97    | 81    | 72    | 5,370  |
| 75              | 58    | 93    | 124   | 104   | 135   | 137   | 91    | 62    | 52    | 41    | 33    | 21    | 10    | 961    |
| 80              | 334   | 516   | 721   | 726   | 804   | 838   | 764   | 631   | 460   | 387   | 278   | 230   | 216   | 6,905  |
| 85              | 14    | 37    | 49    | 59    | 95    | 93    | 85    | 106   | 63    | 74    | 38    | 33    | 35    | 781    |
| 90              | 97    | 164   | 308   | 368   | 467   | 675   | 802   | 796   | 680   | 534   | 437   | 376   | 349   | 6,043  |
| 95              | 4     | 11    | 12    | 25    | 39    | 50    | 82    | 79    | 67    | 68    | 38    | 39    | 7     | 561    |
| 100             | 3     | 6     | 13    | 26    | 87    | 124   | 189   | 305   | 280   | 287   | 247   | 197   | 197   | 1,933  |
| 105             |       |       |       | 4     |       | 7     | 16    | 21    | 33    | 25    | 27    | 23    | 20    | 181    |
| 110             |       |       | 3     | 8     | 12    | 29    | 61    | 105   | 108   | 115   | 11    | 111   | 76    | 745    |
| 115             |       |       |       |       |       | 2     |       | 5     | 9     | 4     | 4     | 6     | 8     | 36     |
| 120             |       |       |       |       |       | 3     | 17    | 38    | 43    | 43    | 56    | 51    | 43    | 302    |
| 125             |       |       |       |       |       | 1     | 2     | 3     | 4     | 2     | 4     | 4     | 1     | 1      |
| 130             |       |       |       |       | 1     | 2     | 9     | 11    | 19    | 23    | 24    | 19    | 23    | 131    |
| 135             |       |       |       |       |       |       |       |       |       | 2     |       |       |       |        |
| 140             |       |       |       |       |       | 1     | 3     | 6     | 2     | 8     |       | 6     | 4     | 37     |
| Over 140        |       |       |       |       | 1     |       | 1     | 4     | 1     |       | 3     | 2     | 1     | 13     |
| Total           | 1,425 | 2,057 | 2,427 | 2,111 | 2,538 | 2,666 | 2,652 | 2,487 | 2,085 | 1,789 | 1,490 | 1,185 | 1,117 | 26,281 |

miniature series could be made according to different principles.

- 1 Selection on the basis of the blood pressure.
- 2 Selection on a basis other than blood pressure.

The object was to obtain a series that would involve as little expense as possible and that would not be so large that it would overwhelm the capacity of the personnel, material, and premises available.

Selection according to the first method could be carried out with the series grouped by stratification of blood pressure.

The question was whether the miniature series should be selected according to the systolic blood pressure, the diastolic or a combination of both the systolic and the diastolic blood pressures. Increased diastolic blood pressure is as a rule combined with increase in the systolic, while an increase in the systolic, to a lesser extent, leads to an increase in the diastolic.

Selection according to the diastolic blood pressure would be practical if one wished in particular to describe the manifestations of diastolic hypertension. On the other hand it is also desirable to be able to examine the conditions in systolic hypertension. Some authors, for example Page & Corcoran (168) suggest that early stages of hypertension ('prehypertension') can present with transient and irregular episodes of elevated chiefly systolic blood pressure. If this hypothesis is correct it would be practical to select the series according to the systolic blood pressure.

The other main aim — that of using the series for a prognostic study — made it necessary that the selection should be made in such a way that all levels of blood pressure and all types of hypertension would be included.

Thus one was left with a *selection based on stratification by systolic blood pressure*

The selection could be made in two ways either as a selection with a common selection percentage for the whole series,

or as a selection with varying selection percentages depending on the total number of individuals in the different blood pressure groups.

To illustrate this more closely the primary series will be considered classified according to the systolic blood pressure (see Tables 4.1 and 4.2). Here the distribution is given with class intervals of 5 mm Hg for each age group. By adding together the blood pressure groups into groups with larger class intervals, and the 5-year classes to 10-year classes, one gets a simpler distribution. The choice of 150 mm Hg has been made as a practical dividing line between pathological and normal blood pressures. With an arbitrary selection of a class interval of 30 mm the following groups were obtained 150-175, 180-205 and 210-235 240-265 and 270-295 mm Hg. As the total number of individuals in the 3 highest blood pressure groups was so low these groups have been combined to form an open class  $\geq 210$  mm Hg. The blood pressure levels below 150 mm Hg which will often hereafter be referred to as the 'normal material' was also combined to form an open class.

The term 'normal material' in this connection is not an indication of what should really be considered a normal blood pressure, but refers to the individuals who were called in by a letter worded in a different way from that used for those with a blood pressure over 150 mm. Hg (see p. 46).

A systolic grouping of the series into these blood pressure groups showed the following distribution (see Table 4.3).

The total number of individuals is given for men and women in 10 years groups, except for the youngest age group, 15 years, and the oldest.

In the blood pressure group  $\geq 210$  mm Hg considerably more women than men are to be found in the higher age groups.

In the blood pressure groups 180-205 and 150-175 mm Hg more men below 40

Table 4.3. The distribution of individuals according to sex, age and blood pressure  
Percentage selection used in the different groups

| Systolic BP |                      | Age groups |       |       |       |       |      | Total  |
|-------------|----------------------|------------|-------|-------|-------|-------|------|--------|
|             |                      | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 |        |
| ≥ 210       | Males                |            | 4     | 21    | 77    | 159   | 147  | 588    |
|             | Females              |            | 5     | 58    | 214   | 439   | 491  | 1,202  |
|             | Percentage selection |            | 100   |       | 25    | 10    |      |        |
| 180-205     | Males                | 23         | 51    | 144   | 281   | 377   | 356  | 1,212  |
|             | Females              | 2          | 39    | 251   | 703   | 852   | 816  | 2,663  |
|             | Percentage selection | 100        |       | 25    | 10    |       |      |        |
| 150-175     | Males                | 676        | 893   | 1,028 | 1,190 | 899   | 550  | 5,226  |
|             | Females              | 349        | 707   | 1,598 | 1,972 | 1,386 | 860  | 6,872  |
|             | Percentage selection | 25         | 10    | 5     |       |       |      |        |
| ≤ 145       | Males                | 3,076      | 2,799 | 2,351 | 1,552 | 662   | 505  | 10,725 |
|             | Females              | 5,280      | 4,031 | 3,355 | 1,666 | 595   | 235  | 15,162 |
|             | Percentage selection | 1          |       |       |       | 5     |      |        |

years of age are found while women predominate above this age.

On the other hand, in the blood pressure group ≤ 145 mm Hg the women are in the majority until the age of 50 years. In the higher age groups the frequencies tend to equalise.

The selection had to be made in such a way that the series was sufficiently large to ensure that the observations and the conclusions drawn from them were based on as firm a foundation as possible. It was impossible to estimate beforehand how large this miniature series should be, as the problems that it was hoped to solve were so varied. It was quite impossible to estimate beforehand an approximate size for this series from the literature. Such calculations must be based on the total number of variables, the degree of variation, and the margin of certainty that is demanded.

Preliminary investigations were difficult to arrange.

An average of 30 individuals in each

of the 24 groups would mean a total of 1,540 individuals, both sexes included. A series consisting of 1,500-1,800 would be the most one could manage.

If one were to select the subsample with the same selection percentage for the whole of the material, there would be too few individuals in the higher blood pressure groups in comparison to the lower

A selection percentage of 5 would thus give a miniature series of about 2,200 individuals assuming a 100 % attendance and, if the attendance were 80 % about 1,750 individuals. In this miniature series the expected total of individuals under 50 years with a blood pressure of over 210 mm would be only 4 men and women taken together.

As a result one could hardly have drawn any conclusions from the data obtained from groups with high blood pressure.

Selection of the miniature series could therefore only be made by using different selection percentages in the different age

and blood pressure groups in the two sexes. The skew distribution with the greatly varying totals in the different groups results in a variation of the selection percentage from 100 % to 1 %. Thus one had to examine everyone with a systolic blood pressure of over 210 mm Hg up to the age of 50 years and all up to 40 years in the blood pressure groups 180-205 mm Hg. In the remaining age and blood pressure groups it was convenient to use a lower selection rate as is shown in Table 4.3 and Figure 4.2.

It is evident from the Figure that the selection varied within the same age group. It would have been more practical for the selection to have been the same in groups of the same age, but even this would have been infeasible. This is evident from Table 4.3.

One of the aims is to compare the findings in men to those in women. Therefore the same rate of selection has been used consistently in the two sexes within the same age and blood pressure groups. Such a comparison between the two sexes is of value, as most of the series published to date have been marked by a greater or lesser degree of selection as regards sex.

A second important point must also be considered in the selection — the use of the series for a prognostic study. Therefore the total number of individuals in the younger age groups is relatively greater than that in the older.

The total number of individuals that could be examined in using this method proved to be 1,964 (see Table 4.4).

The second alternative, a selection regardless of the blood pressure distribution was also considered. The selection of the individuals could, for example, be made according to the serial number on the card at the mass X-ray examination. A selection of this type would also demand a very large series in the same way as that using a common selection percentage for the whole series. In order to obtain a hypertension series of a useful size, so many individuals would have had to be exam-

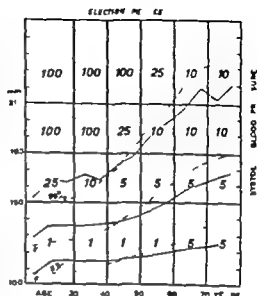


Fig 4.2 Selection percentage used in the various age and blood pressure groups.

ined that the task would have become impossible for one man. This alternative was therefore dropped. On the other hand, such a principle would certainly be fruitful in conjunction with team-work of the type of the Framingham Investigation (47).

Much space has intentionally been devoted to the different alternatives available for the selection. The selection of the series on the basis of the level of the blood pressure is an important and salient point in this work. It should be realized that the blood pressure, at the mass X-ray examination, was taken as an outpatient measurement once, first by palpation, then by auscultation. A random selection was then made on the basis of stratification of these blood pressure levels.

### The method of selection and the material selected

In the field of medicine and particularly in public health research the sampling of human population has become of in-

creasing importance in recent years. This applies in particular to studies of the incidence and the prevalence of certain groups of illnesses, including cardiovascular diseases. Typical examples are the Pneumoconiosis Research Unit in South Wales, with 1 to 90 sampling of the population and the Framingham Study in Massachusetts, U.S.A. (48)

There are several publications on modern methods in the sampling of human populations in which the principles are discussed in detail to give a survey of this large amount of literature, however lies outside the scope of this study. When successful, such studies provide, according to Cochran (40) usable information about the characteristics of a large group of people quickly and moderately cheaply.

In studies of this type it is usual to take a random selection from a census, according to local districts in a town or according to blocks of flats or even smaller units. It is not uncommon to draw samples in two steps (subsampling or two-stage sampling). This study can to some extent be considered as a two-stage sample however the first stage (mass-radiography) is not a random sample in a strict sense.

The random selection can be made in different ways, but the most reliable method of selection is the use of random sampling numbers. In this case each number has the same chance of being picked out from the mass.

In this work the individuals were chosen at random from the great mass of cards that were at that time arranged in age groups according to increasing blood pressure levels, classified systolically. The individuals were picked by counting the cards and selecting those corresponding to the numbers that had previously been chosen and listed from the Table of random sampling numbers (Fisher & Yates, 70)

As an example it can be mentioned that in the 50-59 years age group with a systolic blood pressure of 180-203 mm. Hg there were 281 men and 703 women, 984 individuals in all (see Table 4.3). 10 % of this total was to be called in that is to say 28 men and 70 women. All 28 numbers in the Tables of random numbers with figures up to 281 were noted and after that all 70 different numbers up to and including 703. The figures were then arranged in ascending order the cards

Table 4.4 Series randomly selected  
Number of individuals in age and blood pressure groups

| Systolic BP 1950 | Sex | Age groups |       |       |       |       |      | Sub-total | Total |
|------------------|-----|------------|-------|-------|-------|-------|------|-----------|-------|
|                  |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 |           |       |
| ≥ 210            | M   |            | 4     | 21    | 19    | 14    | 15   | 73        | 278   |
|                  | F   |            | 5     | 53    | 54    | 44    | 49   | 205       |       |
| 180-205          | M   | 23         | 51    | 36    | 28    | 38    | 33   | 209       | 550   |
|                  | F   | 2          | 39    | 63    | 70    | 85    | 82   | 341       |       |
| 150-175          | M   | 135        | 90    | 52    | 59    | 45    | 28   | 409       | 839   |
|                  | F   | 70         | 70    | 79    | 99    | 69    | 43   | 450       |       |
| ≤ 145            | M   | 30         | 28    | 23    | 20    | 33    | 15   | 149       | 302   |
|                  | F   | 32         | 30    | 33    | 16    | 29    | 13   | 153       |       |
| Total            | M   | 180        | 173   | 132   | 126   | 130   | 91   | 840       | 1,969 |
|                  | F   | 104        | 144   | 228   | 239   | 227   | 187  | 1,129     |       |

counted in succession and those corresponding to the random numbers on the list were selected.

The material that was selected from the mass of cards is shown in Table 4.4

The choice was made in accordance with different selection percentages, as shown in Table 4.3 and Figure 4.2. In this way a grouped miniature series was obtained which had a more equal number of individuals within each cell than the primary series, making a total of 1964 individuals, 1129 women and 835 men.

During the counting of this large group of cards a miscount was made in some of the groups in the normal series. Here there were a particularly large number of cards. In the women's groups 15-29 and 30-39 years with a systolic blood pressure  $\geq 145$  mm Hg 52 and 40 individuals were picked instead of 32 and 30 and among men from 50-59 years 20 instead of 15 individuals were picked. These mistakes were discovered too late to be corrected.

### The way in which the subjects were called in

The individuals selected from the cards were called in by letter. To explain the reason for such a summons a form was made containing among other things, the following

According to the blood pressure measurement taken at the time of the mass X-ray examination in the first half of 1950 your blood pressure was higher than we usually consider to be normal. It is important that this should be investigated more closely. It may be of importance to you at present or in the future.

Dr. Sigurd Humerfelt has offered to give you further examination with regard to this raised blood pressure. Dr. Sigurd Humerfelt works at the Medical Dept., Haukeland Hospital.

The investigation will not involve you in any expense. It will consist of a thorough clinical investigation, and will last from 1 2 3/4 of an hour.

If you telephone to make an appointment at a time convenient for you you will not have to wait.

On this first occasion no propaganda or other publicity was used. It was pointed out that the investigation was voluntary and each individual was told of the programme of the investigation and of its use.

In some cases admission to hospital was necessary as part of the work on the series, for instance in all cases with proteinuria in order to obtain a more accurate estimation of the renal function.

It was realized that the individuals who were examined would inform their nearest family or friends of the details of the investigation and it was of considerable importance that the investigation should not become unpopular. A certain impression had already been gained both from direct and indirect information, that the investigation would be well received by the public.

A definite time table was drawn up for each day and each individual was given a definite appointment. About half of the people attended at the time given, but in the cases where a different appointment was needed this was arranged either by telephone or letter. At first, telephone contact was used, but, as in many cases it proved difficult to make an effective connection, a stamped envelope was sent to each addressee and a written answer was requested in the cases in which it was necessary to change the time of the appointment. A written appointment with the request for a written reply proved to be psychologically correct as in this way one came into closer contact with the individuals and the investigation thus acquired a more personal touch. The character of a mass investigation was, to a certain extent, eliminated. In addition one gained a better impression of the individuals' grounds for refusing to attend at a prearranged time.

Those who refused to attend the first time were approached once more (letter



II) and a stamped envelope was again enclosed. The wording of this second letter was as follows

As you will remember you were called in for a check up on \_\_\_\_\_, but did not attend on this occasion. I am taking the opportunity of writing to you personally to ask you to attend at a new time. I have of my own free will taken upon myself this follow up work, and it is extremely important that the attendance should be as high as possible in these follow up investigations. In an investigation of this type you get — free of cost to yourself, whether you belong to the health service or not — a thorough investigation with regard to the raised blood pressure found previously. This comprises a thorough examination of the heart, with X rays and electrocardiograms, urinary investigations and blood tests. All the investigations will be made by me personally and will take from 1/2 3/4 of an hour

You will be able to arrange either by telephone or by the enclosed letter a time convenient to yourself and thus avoid waiting. May I suggest the following time for you — \_\_\_\_\_? If this time does not suit, or if you have any difficulties in complying with my request could you please let me know either by telephone or in writing (stamped envelope enclosed)

In this way a more personal touch was obtained and this led to a considerable improvement in the attendance as many who had refused to be examined on the first occasion now attended.

Those who had a blood pressure of under 150 mm Hg systolic at the time of the mass X ray examination in 1950 were called in by a letter worded in a different way and on other grounds than those with high blood pressure (letter III). It was pointed out in this letter that the blood pressure was normal and that attendance was requested as a part of a control series.

Between 1 and 2 years ago an extensive medical investigation was started on people who were found to have a raised blood

pressure when measurements were taken at that time. These investigations, comprising over 1,300 people, are now being analysed by the undersigned. For these investigations to be of any research value, however there must be a basis for comparison. This can only be obtained from corresponding investigations on people with a normal blood pressure. At the time of the mass X ray examination it was found that you had a normal blood pressure. To make sure that this is still the case I would like to ask you to come for a routine examination. This will be made by me personally and will last from 1/2-1 hour. The investigation will not involve you in any expense, whether you are a member of the health service or not.

### The scheme of the examination

To make sure that the investigation was done with the same technique a case sheet was worked out with all the questions and investigations entered. It was decided from the first that all the material should be recorded on punch cards (IBM) and the case sheet was fashioned in such a way that there was room for coding.

*The case sheet consisted of the following*

#### *Basic information*

- Name, age, with year and date of birth, address.
- Occupation and place of work. Social conditions, economic and housing conditions.
- Marital status, number of children. Health of children.

*Family history* The health of the parents and siblings, cause of death and age at death where applicable.

*History* Earlier diseases and hospital admissions.

Complications of pregnancy and labour. Information concerning previous blood pressure measurements.

The reaction of the patient to this summons.

### *The symptomatology*

The following questions were asked in each case and when the answers were positive the type of symptom, its degree and duration were specified more closely

Headache.

Dizziness.

Tinnitus.

Psychoneurotic manifestations. Nervousness, depression, insomnia, tiredness, weakness. Visual disturbances.

Encephalopathic phenomena, symptoms of cerebrovascular accident.

Cardiac manifestations

a) angina pectoris.

b) feelings of oppression, cardiac pains, palpitations.

c) dyspnoea on exertion — at rest — nocturnal.

d) Symptoms of cardiac failure, oedema.

Pulmonary manifestations symptoms from the respiratory tract.

Nose bleeding

Climacteric symptoms.

Gastric and/or intestinal upset.

Renal and urinary tract symptoms.

*Notes completed together with the first symptom.*

*Present condition* General examination (stripped to the waist and lying down)

Recording of the general habitus and appearance.

Measurement of height and weight.

Pulse recording

Measurements of the blood pressure sitting, lying, and after half an hour rest.

Cardiac status Localization and character of the apex beat, auscultation

Signs of congestion.

Pulmonary findings.

Abdomen.

Pulsation in peripheral vessels.

Investigation of the reflexes, supplemented by neurological investigation when necessary

*Ophthalmoscopy* after homatropine drops.

*Urine* — investigation of a morning specimen (brought by the patient) or of a fresh specimen

*X-ray* of the heart in 2 planes.

*Electrocardiogram* with standard leads and II unipolar precordial leads.

*Blood tests* for estimation of haemoglobin and Wassermann reaction.

*Supplementary tests* in the cases in which the examination revealed signs of disease or special findings that needed to be studied more closely All patients with proteinuria were followed up by kidney function tests either after admission, or if the patient refused to be admitted as an out patient.

### *Statistical methods*

As presented in Table 4.4 the randomly selected series consists of individuals divided between 24 cells. Although the selection has been made by varying selection percentages to compensate for the great difference in the number of individuals in the primary series, there are still unequal numbers within the cells. In some the numbers are too small (one cell is completely empty) to justify any use of statistical methods, but in most groups the number of individuals should be large enough.

In the following several main types of problems are involved (see Bailey 14)

Problems concerned with the examination of a single sample of measurement and comparisons between two or more samples of measurements. The basic distributions involved are the normal (approximately normal) ones, such as height and weight (chapter V) and blood pressure (chapter VI) or binomial distributions such as marital status (chapter V) and several cardiac signs and symptoms (chapter VII)

Problems concerned with the comparison of observed frequencies with theoretical ones obtained using the  $\chi^2$  test. Contingency Tables with rows and columns are presented (chapter VII)

Problems dealing with correlations of pairs of variables and partial correlation

of sets of more than two variables (chapters VI VIII)

Regression analyses and partial regression analyses are also indicated (chapter VIII)

In the two-way classification of the binomial distributions of cardiac signs and symptoms, presented in chapter VII the  $\chi^2$  test follows the formulae given by Reiersøl (189). This method involves complicated calculations, but the method has been developed for use with punch cards (IBM)

There is a lower limit to the size of sample for which the method is sufficiently reliable. According to Bailey (14) the best rule to follow is that no expected number should be smaller than about 5 although the observed numbers may be lower. If some cells exhibit this undesirable feature certain rows or columns of the Table are amalgamated. The assumption is that the homogeneity within groups is still retained. In all calculations (except one, see Table 7.7) it is also necessary to exclude the youngest age groups (15-29) in both sexes because of the very small number of individuals within the cells with high blood pressure.

The standard formulae used and the calculations of mean ( $\bar{x}$ ) and variance ( $S^2$ ), standard deviation ( $S.D.$ ) and standard error ( $S.E.$ ) follow the general principles.

The levels of significance are taken as follows

$$\begin{array}{ll} 0.01 < P < 0.05 & \text{designated} \\ 0.001 < P < 0.01 & " \\ & P < 0.001 & " \end{array}$$

As a conventional level a  $P$  of 0.05 is taken as significant

## Summary

The aim of the investigation and the plan of study is presented

Representative groups of individuals belonging to both sexes and including all age groups and different blood pressures are selected at random from the primary series (group I)

The present work is a cross-sectional study. The variability of the blood pressure is studied in relation to the casual readings from the 1950 investigation and in relation to rest. Furthermore, cardiac symptoms and signs are investigated, including the subjective symptom of dyspnoea and symptoms indicative of coronary disease, as well as the following cardiac findings: the apex beat, and the auscultatory findings over the heart. The electrocardiographic and radiological estimation of the heart size are studied.

All findings are related to blood pressure and age in both sexes.

The selection of the series has been based on stratification of the systolic blood pressure, using different selection percentages in the different age and blood pressure groups in the two sexes. In this way a grouped series (miniature series or subsample) was obtained which had a more equal number of individuals within each cell than the primary series.

The individuals were selected by random sampling numbers (Fisher & Yates, 70) and included a total of 1,964 individuals, 1,129 women and 835 men.

The way in which the subjects were called in and the scheme of the investigation are described in detail.

The statistical methods used are briefly reviewed.

## CHAPTER V

### General findings

#### The attendance of the population for examination

In chapter IV (Table 4.4) was shown the material, divided into groups, which one hoped to investigate. The letters requesting attendance were sent out and investigation took place from March 1951 in parallel with the mass-radiography and blood pressure measurements in group II in Bergen. The investigation lasted to the end of 1952 and occasional check-ups were made in 1953 when the material was being sorted out and arranged.

The material which had been gathered by the end of the investigation appears in Table 5.1 divided into sex, blood pressure, and age groups.

An estimation of the attendance is given in Table 5.2

The percentage attendance has been calculated for both sexes for the same age and blood pressure groups as in the previous Tables.

It is necessary to consider the series after dividing it into pathological (blood pressure  $\geq 150$  mm Hg) — and normal material ( $\leq 145$  mm Hg) because of the different wording of the summoning letters (compare chapter IV, p. 46)

The attendance of the pathological group was relatively good. In all 81 attended for the investigation, and the attendance was somewhat better for men (83 %) than for women (79 %)

Table 5.1 Study group  
Number of individuals in different age and blood pressure groups

| Systolic BP 1950 | Sex | Age groups |       |       |       |       |           | Sub-total | Total |
|------------------|-----|------------|-------|-------|-------|-------|-----------|-----------|-------|
|                  |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | $\geq 70$ |           |       |
| $\geq 210$       | M   |            | 3     | 20    | 24    | 8     | 10        | 65        | 229   |
|                  | F   |            | 5     | 47    | 44    | 32    | 36        | 164       |       |
| 180-205          | M   | 22         | 40    | 32    | 21    | 33    | 22        | 170       | 397   |
|                  | F   | 1          | 30    | 44    | 43    | 56    | 51        | 227       |       |
| 150-175          | M   | 108        | 70    | 54    | 44    | 46    | 18        | 340       | 715   |
|                  | F   | 42         | 65    | 94    | 93    | 51    | 30        | 375       |       |
| $\leq 145$       | M   | 19         | 11    | 20    | 19    | 22    | 7         | 108       | 209   |
|                  | F   | 14         | 22    | 11    | 14    | 20    | 12        | 101       |       |
| Total            | M   | 149        | 134   | 126   | 108   | 109   | 57        | 683       | 1,550 |
|                  | F   | 57         | 122   | 204   | 196   | 159   | 129       | 867       |       |

Table 5.2. Study group  
Percentage attendance

| Systolic<br>BP<br>1950 | Sex | Age groups |       |       |       |       |      | Sub-<br>total | Total         | Grand<br>total |
|------------------------|-----|------------|-------|-------|-------|-------|------|---------------|---------------|----------------|
|                        |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 |               |               |                |
| ≥ 210                  | M   |            | 75    | 93    | 91    | 91    | 63   | 88            | Males<br>83   | 81             |
|                        | F   |            | 100   | 90    | 83    | 73    | 73   | 80            |               |                |
| 205-180                | M   | 91         | 78    | 89    | 75    | 90    | 61   | 81            | Females<br>79 |                |
|                        | F   |            | 77    | 70    | 64    | 65    | 63   | 67            |               |                |
| 175-150                | M   | 81         | 88    | 88    | 86    | 86    | 67   | 84            |               |                |
|                        | F   | 60         | 93    | 94    | 94    | 79    | 70   | 87            |               |                |
| ≤ 145                  | M   | 63         | 75    | 87    | 95    | 67    | 47   | 77            |               |                |
|                        | F   | 47         | 74    | 58    | 87    | 69    | 92   | 66            |               |                |

If one calculates the percentage attendance after having subtracted those who, between the mass investigation in 1950 and this one had died or moved from the town or whose address the post office could not trace one finds a total attendance of 85 %.

If one considers the different age and blood pressure groups more closely one finds some variations. The attendance is, on the whole, best in the groups where the blood pressure is the highest. An exception occurs in the attendance of women in the over 40-year age group with a blood pressure of between 180-205 mm Hg, in which the attendance was distinctly worse than for men in the corresponding age group. The average attendance was only 67 % in this blood pressure group while 81 % of the men attended. The poorest attendance of all is found among the women in the age group (15-29) with a blood pressure of 150-175 mm Hg.

When one considers the attendance in the different age groups without regard to the blood pressure one sees that the attendance was on the whole worse in the highest age groups (70 years and over). This is probably due to the reasons that were given on p. 34.

The attendance of the normal material was worse than that of the patho-

logical being on an average only 70 %. The men here also showed a better attendance than the women in all younger and middle age groups. The worst attendance rate was for the youngest women (age group 15-29) of whom only 47 % attended, while the men in the same group showed a rate of 63 %. On the other hand the normal material was relatively well represented in the highest age groups of women in contrast to men.

### Discussion

There is a difference in the attendance at the mass-radiography and blood pressure measurements in 1950 in comparison to the attendance at this clinico-epidemiological investigation in 1951-52. The men consistently showed a worse attendance at the first investigation while their attendance at this repeat investigation was better than that of the women. It is difficult to give any definite reasons for this, but the following conditions could be of significance. The public could attend the mass-radiography investigation when they liked as long as they went on the day the street or the district was scheduled for examination whereas the individuals in this investigation were asked to attend at a given

time, and the investigation was known to take about an hour. The measurements in 1950 took considerably less time rarely more than 15 minutes. As it was already known that the attendance had been worse for men than for women in 1950 care was taken to see that the men were asked to attend in the afternoon after working hours, so that loss of working time would be reduced. The morning was for the most part reserved for the women. It is possible that this in itself explains why the attendance was better for men than for women.

The reason that the attendance of the younger women was so bad, is probably that some of them had families with small children and they could not easily get away or find time for an investigation of this type. Another point is that all young people undergo more regular health examinations, as has been mentioned in the previous chapter.

It is natural that the attendance of the normal material should be somewhat worse. The individuals with a blood pressure of under 150 mm Hg were asked to attend in a letter which was worded differently from that sent to those with blood

pressures of over this value. It was, among other things, pointed out that they had a normal blood pressure, but that their attendance would be greatly appreciated as part of a control investigation (see p. 46). It is therefore reasonable that fewer people came in response to this request.

## The reliability of the study group

### 1 Blood Pressure Distribution

In chapter III (p. 31) the attendance for mass-radiography and blood pressure measurements in 1950 has been discussed. In addition the attendance of the study group at the 1951-52 investigation was worked out in the previous section.

To what extent does the study group give a true picture of the blood pressure distribution in the population of the city of Bergen? Is the random sampling technique used correct?

The study group consists of random samples taken from the mass investigation, after it had been divided into groups. The question which will be answered is how far the distribution of the blood pressure within the different classes of the study

Table 5.3. Ratio  $t_i$  for the different groups in the study group

The ratio  $t_i = \frac{1}{n_i}$  gives the number of individuals in group  $i$  of the primary series represented by one individual in the study group

| Systolic BP 1950 | Sex | Age groups |         |         |         |        |        |
|------------------|-----|------------|---------|---------|---------|--------|--------|
|                  |     | 15-29      | 30-39   | 40-49   | 50-59   | 60-69  | ≥ 70   |
| ≥ 210            | M   |            | 1.333   | 1.050   | 4.278   | 10.692 | 14.700 |
|                  | F   |            | 1.000   | 1.128   | 4.756   | 13.719 | 13.639 |
| 180-205          | M   | 1.095      | 1.275   | 4.500   | 13.381  | 11.868 | 16.000 |
|                  | F   | 1.000      | 1.300   | 5.705   | 13.622  | 13.491 | 15.692 |
| 150-175          | M   | 6.202      | 12.757  | 19.057  | 27.045  | 19.543 | 30.556 |
|                  | F   | 8.310      | 10.877  | 17.000  | 21.204  | 27.176 | 28.667 |
| ≤ 145            | M   | 170.889    | 144.950 | 117.060 | 80.632  | 33.310 | 33.310 |
|                  | F   | 77.143     | 175.261 | 176.579 | 119.000 | 25.958 | 25.958 |

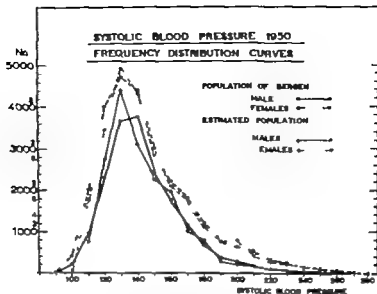


Fig. 5.1 Systolic blood pressure. Frequency distribution curves of the Bergen series (group 1) compared with an estimated (theoretical) population based upon the study group

group deviates from the distribution in the corresponding classes in the primary series. Two factors become prominent

- a) the sampling error
- b) the non-attendance.

If  $\Lambda$  represents the total number of individuals in group  $i$  of the primary series, and  $n_i$  is taken to be the corresponding total in the study group, then the

$$t = \frac{\Lambda}{n_i}$$

ratio gives the number of individuals in group  $i$  of the primary series represented by one individual in the study group. Table 5.3 gives  $t$ , for the different groups in the study group.

From this Table  $t$  can be seen that  $t$  is 1 or nearly 1 in the groups where all the individuals have been examined, whereas  $t$  is very high in the groups where only 1 per cent of the population has been examined.

A theoretical distribution can be worked out on this basis and can be compared with the distribution in the primary series.

The two distributions are given in Fig 5.1

It is found that the distribution in the primary series and in the theoretical one corresponds very closely in both sexes when the blood pressure is higher than 150 mm Hg. There are some deviations at the lower pressures, but on the whole the curves follow each other fairly well, without large or consistent deviations. The normal material was chosen with selection percentages of only 1 and 5 and the deviations shown by the distribution curves must be seen against this background.

In the distribution curves (Fig 5.2) the primary series and the theoretical distribution are presented, with the series divided up into 4 age groups. There is relatively good agreement in all age groups with high blood pressure. Among women in the age group 15-29 however there is a consistent deviation of the lower blood pressures. The 110 and 120 values are fewer than the number shown in the primary series on the other hand, the 130 mm values show an increase. Further

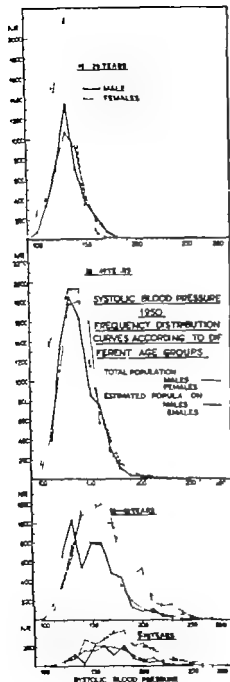


Fig. 5.2. Systolic blood pressure in the different age groups.

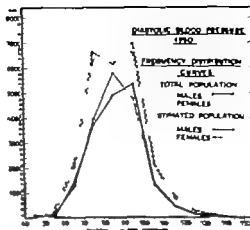


Fig. 5.3. Diastolic blood pressure. Frequency distribution curves of the Bergen series (group 1) compared with an estimated (theoretical) population based upon the study group.

in the age groups 30-49 one finds a levelling out of the distribution curve around the 130-140 mm values. There are no consistent differences in the highest age groups.

As has been mentioned earlier the study group was chosen on the basis of the systolic blood pressure. What is the distribution of the diastolic blood pressure in the corresponding age groups? Has this selection, based upon the systolic blood pressure, caused any skewness in the distribution of the diastolic blood pressure?

With the help of the same ratios the distribution of the diastolic blood pressure has been worked out. This is shown in Fig. 5.3.

The primary series shows an almost normal distribution however the curves are somewhat skewed to the right, as there is an excess of high diastolic values. The theoretical distribution agrees well with this. In both sexes the curves show a levelling out around the 80-85 values, otherwise the distribution curves fall nicely together.

On dividing the series into the same 4 age groups one finds that the levelling out



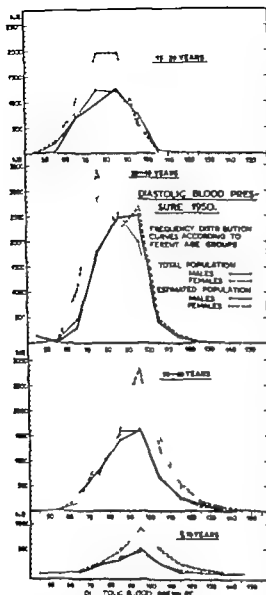


Fig. 5.4 Diastolic blood pressure in the different age groups.

corresponding to the 80-85 mm values makes itself felt mainly in the two youngest age groups. Apart from this the primary series and the theoretical distribution agree well. This is apparent from Fig. 5.4

**Conclusion** The theoretically calculated distribution of the systolic and diastolic

blood pressures agree fairly well with the distribution of the blood pressure in the primary series. When divided into age groups the material also shows satisfactory agreement in the higher blood pressure, whereas some deviations are found in the lower pressures and in the younger age groups.

Two factors enter into this method of calculation. Selection has the greatest influence on the ratio and shows considerable variation, from 1 % to 100 % of the population in the different groups. The influence of the non-attendance seems to be less. This will be discussed below.

#### *Comparison of the blood pressure distributions in the study group and in the group of non-attenders*

To find out if the non-attenders have caused any deviations in the blood pressure distribution in the study group, a comparison has been made between the blood pressure distributions in the two groups. All the above-mentioned subgroups were combined and the frequency distribution of the systolic blood pressure and of the diastolic blood pressure, as measured at the mass investigation in 1950 was worked out for men and for women.

In order to be able to compare the groups of those who did not attend (419 individuals) with those who were investigated (1,550 individuals) the distribution is given as a percentage (see Fig. 5.5 and 5.6)

The distribution of the systolic blood pressure gives in both sexes irregular curves, with the highest points corresponding to 150 and 180 mm Hg. This is due to the subgrouping of the Bergen material (primary series) with different selection rates with regard to age and blood pressure (see Table 4.3)

Such distributions in which all the subgroups have been combined are partly hypothetical. Nevertheless they are useful to illustrate the influence of attendance

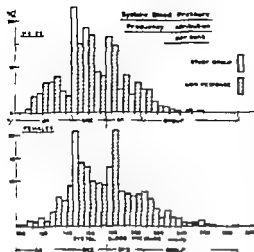


Fig 5.5. Frequency distribution of systolic blood pressure for males and females of the study group (white rectangles) and the non-attendance group (hatched rectangles)

The distribution curve for the men is fairly similar for the 2 groups except for the lower frequency of the 150 mm values in those who did not attend. In women one sees that the frequency of those with a blood pressure of 180 mm is greater in those who did not attend than in those who did. On the other hand, one finds that the frequency of the 150 mm values is somewhat less. These differences are not considerable and are most likely due to the poor attendance in these blood pressure groups (see p 50).

On analysing the distribution of the diastolic blood pressure in the same way one finds that the curves show good congruence in both sexes. The distribution is almost symmetrical, with, however a slight skew to the right. This fact, that by using a method of selection based on a stratification of the systolic blood pressure with varying selection percentage, one obtains an approximately normal distribution of the diastolic blood pressure, has been mentioned earlier (p. 53).

## Conclusion

The calculations show that essential skewness of the blood pressure distribution of the study groups does not result from the non-attendance. There is, however a small deviation in the distribution of the systolic blood pressure in the women.

## 2. Height and Weight Distributions

*A comparison of mean height and weight in the study group and Group II of the Bergen population*

The question arises whether it is possible to estimate the representativeness of the study group by other parameters than the blood pressure.

Measurements of height and weight were not included in the 1950 investigation of group I but in the 1951 survey of group II (southern districts of the city) these measurements were taken.

Assuming that height and weight show the same frequency distributions according to age in the two groups, it should be

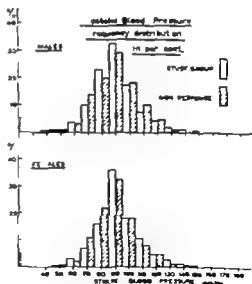


Fig 5.6 Frequency distribution of diastolic blood pressure for males and females of the study group (white rectangles) and the non-attendance group (hatched rectangles)

possible to compare the height and weight distributions in the study groups with those in group II. It has previously been shown by Bøe, Humerfelt & Wedervang (30) that height alone has a negligible effect upon blood pressure.

The correlation between blood pressure and weight is low: systolic pressure increases only about 3 mm for every 10 kg increase in weight, and diastolic pressure only 2 mm.

Therefore it should be possible to use height and weight determinations to estimate the representativeness of this series.

A comparison of the height between this series and group II in relation to age, for each sex, is seen in Table 5.4.

In women the mean height in the study group is higher in all age groups except the oldest.

There is a significant difference at the 5% level between the mean height in the age groups 30-39 and 40-49 years. In men there is a significant difference in the youngest group, the 50-59 group, and in the oldest age group. However it is more

striking that there is a linear trend in the differences between mean heights in men, changing from a positive difference in the younger to a negative difference in the older age groups.

In the same way there is a significant difference between the mean weights (see Table 5.5) in women in the same age groups as for height. In men there is a significant difference in most age groups.

The differences in the mean weights in men also show a linear trend, as did the differences in mean height. In men this shift from a positive difference to a negative one is clearly seen. The main reason for this is probably the relationship between height and weight. According to Bøe, Humerfelt, & Wedervang (30) an increase in height of 10 cm increases the mean weight of young men by 7.8 kg and the mean weight of young women by 6.1 kg.

The conclusion is therefore that there is a significant difference in height and weight distribution in several age groups in both sexes, compared with the group II sample.

Table 5.4 Differences between mean height in the study group and in Group II of the Bergen population sample

| Age group | Study group |                |       | Bergen group II |                |       | Difference                         |              |
|-----------|-------------|----------------|-------|-----------------|----------------|-------|------------------------------------|--------------|
|           | No.         | $\bar{x}$ (cm) | S     | No.             | $\bar{x}$ (cm) | S     | $(\bar{x}_1 - \bar{x}_2) \pm s.e.$ | Signif. test |
| Female    |             |                |       |                 |                |       |                                    |              |
| 15-29     | 57          | 164.0          | 44.39 | 3,644           | 163.0          | 31.89 | $1.0 \pm 0.88$                     | 1.14         |
| 30-39     | 122         | 162.7          | 34.49 | 3,110           | 161.6          | 31.21 | $1.1 \pm 0.53$                     | 2.08         |
| 40-49     | 204         | 161.5          | 29.73 | 2,778           | 160.1          | 30.75 | $1.4 \pm 0.59$                     | 3.60*        |
| 50-59     | 196         | 159.7          | 29.09 | 2,305           | 159.0          | 31.71 | $0.7 \pm 0.40$                     | 1.75         |
| 60-69     | 159         | 157.6          | 43.33 | 1,331           | 157.3          | 32.93 | $0.3 \pm 0.55$                     | 0.55         |
| 70+       | 129         | 155.7          | 30.71 | 637             | 153.9          | 31.07 | $-0.2 \pm 0.51$                    | 0.39         |
| Male      |             |                |       |                 |                |       |                                    |              |
| 15-29     | 149         | 171.1          | 41.99 | 2,238           | 173.0          | 43.90 | $1 \pm 0.55$                       | 3.75         |
| 30-39     | 134         | 171.9          | 35.98 | 2,232           | 174.4          | 40.66 | $0.5 \pm 0.54$                     | 0.87         |
| 40-49     | 126         | 173.1          | 39.33 | 2,028           | 173.1          | 38.23 | $0 \pm 0.48$                       |              |
| 50-59     | 108         | 170.1          | 48.7  | 1,738           | 171.1          | 39.1  | $-1.0 \pm 0.51$                    | 1.96*        |
| 60-69     | 106         | 168.3          | 39.31 | 1,024           | 169.5          | 35.25 | $-1.2 \pm 0.63$                    | 1.90         |
| 70+       |             | 165.3          | 39.07 | 402             | 168.5          | 36.22 | $3.2 \pm 0.88$                     | 3.64         |

Table 3.5. Difference between mean weight in the study group and in Group II of the Bergen population sample

| Age-group | Study group |                |       | Bergen group II |                |       | Difference                         |              |
|-----------|-------------|----------------|-------|-----------------|----------------|-------|------------------------------------|--------------|
|           | No.         | $\bar{x}$ (kg) | $S^2$ | No.             | $\bar{x}$ (kg) | $S^2$ | $(\bar{x}_1 - \bar{x}_2) \pm s.e.$ | Signif. test |

| Females |     |      |        |       |      |        |                 |       |
|---------|-----|------|--------|-------|------|--------|-----------------|-------|
| 15-29   | 57  | 61.3 | 50.40  | 3,644 | 60.3 | 73.13  | $1.0 \pm 0.94$  | 1.06  |
| 30-39   | 122 | 63.9 | 198.46 | 3 110 | 63.2 | 100.91 | $2.7 \pm 1.28$  | 2.11  |
| 40-49   | 204 | 68.8 | 163.90 | 2 778 | 66.7 | 129.24 | $2.1 \pm 0.92$  | 2.78* |
| 50-59   | 196 | 70.5 | 170.40 | 2,303 | 70.1 | 158.16 | $0.4 \pm 0.97$  | 0.41  |
| 60-69   | 159 | 67.0 | 166.10 | 1,351 | 68.7 | 156.14 | $-1.7 \pm 1.08$ | 1.62  |
| 70-     | 129 | 64.3 | 130.34 | 637   | 64.7 | 138.55 | $-0.4 \pm 1.11$ | 0.96  |

| Males |     |      |        |       |      |        |                 |      |
|-------|-----|------|--------|-------|------|--------|-----------------|------|
| 15-29 | 149 | 72.4 | 72.27  | 2,258 | 68.7 | 78.32  | $3.7 \pm 0.72$  | 3.12 |
| 30-39 | 134 | 72.6 | 90.86  | 2,292 | 71.7 | 78.22  | $0.9 \pm 0.85$  | 1.06 |
| 40-49 | 126 | 74.4 | 96.84  | 2,028 | 72.8 | 95.88  | $1.6 \pm 0.91$  | 1.73 |
| 50-59 | 108 | 71.9 | 103.90 | 1 738 | 74.2 | 119.56 | $-2.3 \pm 1.02$ | 2.23 |
| 60-69 | 108 | 70.9 | 145.60 | 1,024 | 73.6 | 125.39 | $-2.7 \pm 1.21$ | 2.23 |
| 70-   | 55  | 65.4 | 85.89  | 502   | 72.5 | 128.91 | $-6.9 \pm 1.35$ | 5.11 |

### 3 Marital Status according to Age

*A comparison of marital status in the study group and in the population of the City of Bergen*

An estimation of the representativeness of the study group can also be made by comparing marital status in this series with that of the Bergen population.

However this assumes that marital status has only a negligible influence upon blood pressure.

It has previously been shown by Humerfelt & Wedervang (103) and by Mjall & Oldham (151) that marital status and the family size have a slight effect on systolic and diastolic pressures. Thus Humerfelt & Wedervang found that the mean systolic and diastolic pressures were slightly higher (4-5 mm Hg systolic and 1-2 mm Hg diastolic) in the group of unmarried women and in married women with 0 or 1 child than in women with 2 or more children. The prevalence of hypertension, defined as systolic  $\geq$  170 mm Hg, was significantly higher in women with 0 or 1 child

Furthermore, Mjall & Oldham found a relationship between blood pressure and parity in both sexes. The regression for systolic scores in women aged 15-45 represented a drop in score of 2.6 mm Hg for each child and for diastolic scores the drop was 0.5 mm Hg.

These effects seem to be relatively small in relation to blood pressure variations in this grouped series. Therefore it should be reasonable to use the marital status to estimate the representativeness.

The percentage distribution of married, unmarried, and single in the population of Bergen in 1932 (21) and in this series is presented in Table 3.6 and illustrated in Fig. 5.7.

There is a clear difference in the 15-29 age group in both sexes. Otherwise there seems to be relatively good agreement.

There is a slight difference in the distribution between the two sexes. While married women have attended less frequently and unmarried women slightly more frequently (except for the youngest and oldest age groups) the opposite has

Table 5.6. *Marital status according to age*

A comparison of marital status in the study group and in the population of the City of Bergen (1952)

| Age     | City of Bergen           |         |                     |             | Study Group |              |                |             |                            |
|---------|--------------------------|---------|---------------------|-------------|-------------|--------------|----------------|-------------|----------------------------|
|         | Total<br>popula-<br>tion | Married | Unmar-<br>ried<br>• | Others<br>% | No.         | Married<br>• | Unmar-<br>ried | Others<br>• | $\chi^2$ test<br>(1 d. f.) |
| Females |                          |         |                     |             |             |              |                |             |                            |
| 15-29   | 11,940                   | 30.3    | 68.6                | 1.1         | 57          | 47.4         | 50.9           | 1.7         | 14.55                      |
| 30-39   | 9,026                    | 72.2    | 23.6                | 4.2         | 122         | 68.0         | 27.9           | 4.1         | 1.03                       |
| 40-49   | 9,118                    | 67.7    | 23.9                | 8.4         | 204         | 66.7         | 28.4           | 4.9         | 2.32                       |
| 50-59   | 8,329                    | 57.1    | 27.4                | 15.5        | 196         | 56.1         | 29.1           | 14.8        | 0.16                       |
| 60-69   | 5,737                    | 44.3    | 27.9                | 27.8        | 159         | 39.6         | 38.4           | 22.0        | 5.66                       |
| ≥ 70    | 4,747                    | 23.5    | 37.5                | 49.0        | 129         | 27.1         | 27.1           | 45.8        | 0.77                       |
| Male    |                          |         |                     |             |             |              |                |             |                            |
| 15-29   | 10,667                   | 22.2    | 77.3                | 0.5         | 149         | 46.3         | 53.7           |             | 33.34                      |
| 30-39   | 8,240                    | 75.4    | 1.7                 | 2.9         | 134         | 78.9         | 20.9           | 2.2         | 0.23                       |
| 40-49   | 7,517                    | 81.9    | 13.8                | 4.3         | 126         | 84.1         | 12.7           | 3.2         | 0.43                       |
| 50-59   | 6,565                    | 81.1    | 12.1                | 6.8         | 108         | 86.1         | 8.3            | 5.6         | 4.17*                      |
| 60-69   | 4,141                    | 75.3    | 10.5                | 14.2        | 109         | 75.2         | 16.5           | 8.3         | 4.83*                      |
| ≥ 70    | 2,636                    | 55.9    | 9.5                 | 34.6        | 57          | 54.4         | 8.8            | 36.8        | 0.23                       |

As long as some of the individuals occur in both samples, the condition of independency is not quite fulfilled. However the failure will be minimal, as the present series forms a small part of the primary series.

happened in men in nearly all age groups.

The difference in the distributions in the two series has been evaluated statistically using the  $\chi^2$  test. (As the size of the group 'Others' is dependent on the sum of the first two groups the degree of freedom is 1)

As expected there is a highly significant difference in the youngest age group in both sexes. Otherwise there is a significant difference on the 5% level in the 60-69 age group in both sexes and in the 50-59 in men.

#### Conclusion

When comparing this series and the Bergen population series a significant difference in the distribution of marital status has been found in two age groups in women and in three age groups in men.

#### Discussion

The object of working out the blood pressure distributions, as presented in this chapter has been to compare the distribution in this series with that of the parent population. Although the main purpose of this investigation has been to select a series with all varieties of blood pressure, it is of importance to estimate the representativeness from factors other than the blood pressure. Therefore the distribution of height, weight, and marital status has been worked out.

Occupation is also an important factor but because of the great difference in the selection rates in the different age and blood pressure groups this would be of no use as the Bergen data on the occupation in the population are not arranged according to age.

It is concluded that there is a significant

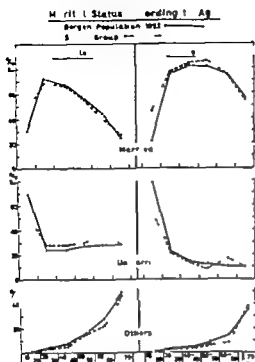


Fig. 5.7 A comparison of the percentage distribution of married, unmarried and single in the study group and in the population of the City of Bergen.

difference in the height and weight distribution in several age groups in both sexes. Such a conclusion is only valid if the hypothesis is true that height and weight distributions in group I and group II of the Bergen population are the same.

As mentioned before, group I includes the central and northern parishes of the town, while group II covers the southern parts. There was previously a difference in the social structure in the population in these two areas. However during the last decade this difference has nearly disappeared. According to the Annual Statistics of the City of Bergen 1953 (21) 45.3 % of the male population and 30.4 % of the female population of group I were labourers. The corresponding figures in group II were 34.8 % and 24 %. Furthermore, the professional groups were smaller

in group I in men 14.3 % and in women 10.0 % compared to 19.5 % and 14.2 % respectively in group II (These data are based upon the number of the electorate at the Parliamentary Election of 1953 and do not include people below 21 years of age.) The data taken from the local municipal election in Bergen 1947 show the same difference in social structure.

Therefore it cannot be excluded that the smaller mean height of men in older age groups in group I could in part be due to the influences of unfavourable nutritional and environmental factors among working-class people in previous years. However a more thorough investigation is needed to confirm this assumption.

When comparing the distribution of marital status a highly significant difference is found in the youngest age group in both sexes. These two groups also show the greatest lapse rate.

It has previously been stated by Bøe, Humerfelt & Wedervang (30) that there was a difference in the distribution of marital status in women in group I and group II (1952). A larger percentage of the female population in group II are married than in group I an average of 54 % to 47 %. In Table 5.6 the comparison is made embracing the total population of Bergen. If the data from group I were used in the calculations, the significant difference (on the 5 % level) in the 60-69 age group in women would be abolished. ( $\chi^2$  test 2.79 on 1 d.f.)

On the whole, because of the lack of satisfactory representativeness one must be very careful in drawing general inferences from this series. The conclusions drawn must be restricted to this series. Nevertheless comparison will as far as possible be made with other series drawn from the general population.

### The group of non-attenders

In every epidemiological work it is important to analyse the group of people

who were not seen. There will always be some individuals with whom it is impossible to get into contact. Others are not willing to take part in an investigation of this type, and yet others have plausible grounds for not attending.

A closer study of this series, with elucidation of the reasons for non-attendance, is necessary before the reliability of the study group can be assessed. It could be thought that the non-attendance had led to the skewness in the distribution of the blood pressure in the material that was collected. Further it is possible that a difference could arise in the prevalence of the different symptoms and signs. The non-attendance could in part be due to poor health. This applies most likely to those who live in nursing homes, or homes for old people. One can get information about these people and those who died in the interval between the mass-radiography and this investigation, but they are only few. The bulk of the group, however, is made up of presumably healthy people who are going about their daily work. We have no exact knowledge of the state of their health, apart from the fact that the frequency of the different symptoms and findings must lie somewhere between 0 and 100.

It was tempting to call in new individuals to make up for those who did not attend. But this would have been of no use

as the series would have grown in size without becoming more representative.

In this series we know the results for 81 % of the pathological subjects ( $\geq 150$  mm Hg) and for 70 % of the normal material ( $\leq 145$  mm Hg).

As has been mentioned before a written request was sent to every one of the individuals selected. A stamped reply form was enclosed to be used to state the reason for non-attendance. A great deal of trouble was taken to include those who did not attend on the first occasion. Consequently the letters requesting their attendance were sent out twice. In those cases where it was stated that a doctor had been consulted information was sought from him. Similarly hospitals, homes for old people, and nursing homes were consulted. Information on deaths was obtained from the City of Bergen Health Office.

Next follows a summary of the groups of people who did not attend. In all these amounted to 419 individuals, 325 of whom had a systolic blood pressure  $\geq 150$  mm Hg. This material is arranged in Table 5.7.

The Table shows the sex distribution of the non-attenders divided into 6 groups.

1 *Deaths* In all, 17 individuals, 3 men and 14 women died in the interval between the mass investigation in 1950 and this investigation, i. e. 4 of those who did not attend. The age distribution is shown in Table 5.8.

Table 5.7 Non-attendance  
Distribution of individuals according to sex

| Group | Reasons                   | Males |          | Females |          | Total |          |
|-------|---------------------------|-------|----------|---------|----------|-------|----------|
|       |                           | No.   | Per cent | No.     | Per cent | No.   | Per cent |
| 1     | Dead                      | 3     | 2        | 14      | 5        | 17    | 4        |
| 2     | Old age and nursing homes | 2     | 1.5      | 7       | 2.5      | 9     | 2        |
| 3     | Left Bergen permanently   | 12    | 9        | 21      | 7.5      | 33    | 8        |
| 4     | Address unknown           | 19    | 14       | 20      | 7        | 39    | 9        |
| 5     | Reason given              | 49    | 36       | 134     | 47       | 183   | 44       |
| 6     | No reason given           | 51    | 37.5     | 87      | 31       | 138   | 33       |
|       | Total                     | 136   | 100      | 283     | 100      | 419   | 100      |

Table 5.8. *Dead*  
Distribution by sex and age

|       | Subtotal |         | Total |
|-------|----------|---------|-------|
|       | Males    | Females |       |
| 40-49 |          | 1       | 1     |
| 50-59 |          | 1       | 1     |
| 60-69 |          | 3       | 3     |
| ≥ 70  | 3        | 9       | 12    |
| Total | 3        | 14      | 17    |

The cause of death and its relationship to the blood pressure at the mass investigation in 1950 can be seen from Table 5.9

All those dying of apoplexy were over 75 years of age. There was no predominance of high blood pressure among those who died. The numbers, however are too small for closer analysis.

2. *Homes for old people and nursing homes*  
Nine of the non-attenders, 2 men and 7 women, were living in nursing homes or homes for old people. All were over 65 years of age. Both men had systolic and diastolic hypertension and had signs of heart failure in addition to senile dementia. Among the women 1 (65 years) was well, but did not wish to attend, and 1 was deaf and dumb the remainder showed signs of senile dementia, and in 2 there were also symptoms of heart failure. All were being attended by a doctor

3. *Those who had moved from Bergen.* An answer was received from 30 of these 33 individuals. All were in full work and all

felt well. Only 1 man and 1 woman had a diastolic blood pressure of over 100 mm Hg and 3 women showed a systolic blood pressure  $\geq 200$  mm Hg. All but 7 were under 50 years of age. Many said that they would go to their local doctor for a further check up. An answer was received from only 5 of these. Pyelonephritis was discovered in 1 of the women, the remainder were all well.

4. *Address unknown* The post-office could not trace the addresses of 9 of the non-attenders. The age distribution shows that they were mostly younger people mainly between 20-35 years, but 5 were over 60 years. These people all lived alone, they were unmarried, living mostly in casual lodging or furnished rooms.

These 4 sub-groups consisted of 98 people, 23% of the non-attenders, or 5% of the selected series.

5 & 6. *The remainder* consisting of 321 individuals, 100 men and 221 women, did not attend in spite of two requests. About 60% of these answered the letters and gave their grounds for non-attendance.

The answers are grouped according to their own statements

a) *No opportunity* ('not time — does not suit — out of town') These grounds were given by 16 men and 28 women. The age distribution was even in all classes over 30 years. The blood pressure distribution showed no important deviations only 4 people had a systolic blood pressure of over 210 mm, of these 3 individuals were over 70 years old.

Table 5.9. *Causes of death related to age and blood pressure*

| Systolic BP 1950 | Heart |   | Cerebral |   | Cancer |   | Infection |   | Subtotal |    | Total |
|------------------|-------|---|----------|---|--------|---|-----------|---|----------|----|-------|
|                  | M     | F | M        | F | M      | F | M         | F | M        | F  |       |
| ≥ 145            |       |   |          | 2 |        |   |           |   |          | 2  | 2     |
| 150-175          |       | 1 |          |   |        | 3 |           |   |          | 4  | 4     |
| 180-205          | 1     |   |          | 4 |        | 1 |           | 1 | 1        | 6  | 7     |
| ≥ 210            |       | 1 | 2        |   |        | 1 |           |   | 2        | 2  | 4     |
| Total            | 1     | 2 | 2        | 6 |        | 5 |           | 1 | 3        | 14 | 17    |



b) *Prefer their own doctor* In all 81 individuals, 25 men and 56 women stated that they were willing to be examined by — or were under the care of — their own doctor. This group can be divided into 2 sub-groups.

*Those without pathological findings* This group is made up of 18 men and 38 women. The age distribution shows that most were between 40 and 69 years of age. The blood pressure distribution in this group showed that very few had high blood pressures. 2 women had a systolic pressure  $\geq 210$  and 3 men  $\geq 180$  mm Hg.

*Known hypertensives* This group consisted of 7 men and 18 women. Most of them were over 50 years of age, however, 4 of the 7 men were under 40 years and 2 of the women under 50 years. All of them had a systolic blood pressure of over 180 mm Hg.

More detailed information from their doctors showed that 2 men and 6 women had signs of cardiovascular disease while 5 of the men and 12 women showed indefinite symptoms, mainly of a nervous type. These investigations were all made by different doctors and were not made in accordance with the plan of this work.

c) *Dread of investigation*. This reason was given by 2 of the men under 30 years of age and 4 of the women in the age group 50-69 years. Both men showed a blood pressure of under 150 mm, while that of the women was  $\geq 180$  mm Hg.

d) *Considered the investigation unnecessary — asked to be exempted — did not wish an investigation of this kind*. In all 4 men and 30 women brought forward these arguments. Two men and 12 women gave as the reason for their refusal that they 'felt completely well' while the rest stated that they were indifferent to, or unwilling to undergo an investigation of this kind. A few gave clearly ethical reasons others pointed out that to consult a doctor was a personal matter, the necessity for which one judges for oneself. The blood pressure and age distribution of this group were not different from the remainder of the material.

e) *Absent because of illness had health problems or hospital admittance*. Eighteen people, 2 of these men and 16 women gave this as their reason. Ten individuals

(all women) were over 70 years of age and in them their great age and feeble health was the cause. In 3 cases pregnancy was given as the hindrance. The hospital admissions had no connection with hypertension. Neither did the blood pressure distribution here show any deviations relative to the age distribution.

Those remaining sent no reply or information and consequently one has no knowledge concerning these individuals. In all they total 51 men and 87 women that is to say 33% of those who did not attend. Sixty-two individuals had a blood pressure  $\geq 150$  mm and they make up 37% of all the 'pathological' material. Seventy-six people had a blood pressure  $\leq 145$  mm and make up 25% of the 'normal' material. The reason for this great difference in both the lapse rate and the number of answers received is probably due to the difference in the wording and in the arguments used in the summoning letters. It seems reasonable to expect that few people will take part in an investigation of this kind when it is pointed out that their blood pressure is normal and that the investigation is to form a part of a control series.

## Summary

The investigation started in March 1951 and lasted until the end of 1952. Occasional check ups were made in 1953.

The percentage attendance varied a great deal. In the pathological group (BP  $\geq 150$  mm Hg) 81% attended in all, men 83% and women 79%. After subtraction of those who died, moved from the town or whose address was unknown, the average attendance was 83%. The attendance in the 'normal' material (BP  $\leq 145$  mm Hg) was on an average 70%.

As in the primary series the attendance was less in the younger and oldest age groups. The reasons for the difference in the attendance in the pathological and normal groups probably lies in the different wording of the summoning letters.

To estimate how far the distribution of the blood pressure in the study group deviates from the distribution in the corresponding classes in the primary series a theoretical distribution has been worked out. It is concluded that the theoretically calculated distributions of the systolic and diastolic blood pressure agree fairly well with that in the primary series. When divided into age groups the series also show satisfactory agreement in the higher blood pressures, whereas some deviations are found in the lower pressures in the younger age group.

In order to compare the blood pressure distribution in the study group with that of the non-attenders a percentage frequency distribution of systolic and dia-

stolic pressure has been calculated. Marked skewness in the distributions does not occur there is, however a small deviation in the distribution of systolic pressure in women.

An estimation of the representativeness has also been made from other factors, such as height, weight, and marital status. It is concluded that several age groups show significant differences in the distributions of these factors. The reasons for the differences and the validity of these comparisons are discussed.

The conclusion is that one must be very careful in drawing general inferences from this series.

Finally a description of the groups of non-attenders is given.

## CHAPTER VI

# The blood pressure measurement

### Abstracts from and comments on the literature

In planning this work the approach and method of taking the blood pressure were carefully considered.

A survey of the literature shows that in most recent epidemiological blood pressure studies the sitting position has been used. In Hamilton *et al.*'s (89) study all readings were taken in the main outpatient hall with the subject seated, usually after 10 to 15 minutes rest. All observations were made by one or other of the authors. In the mass investigation of Master Garfield & Walters (145) the subjects were examined at work. The authors, however do not give an exact account of the position or the method of taking the systolic or diastolic blood pressure. In both the studies of Miall & Oldham (150, 151) the recordings were made in the subject's own home after the subject had been seated for a period of at least five minutes. The same observer made all readings, using the right arm. In Comstock's (44) study all readings were made in the subject's home environment. The subject was seated as comfortably as possible. The determinations were made on the right arm.

In the recent study of Karpinen (110) the recordings were made in the sitting or recumbent position according to the principles laid down in the revised mobilization regulations.

In the mass investigation of Bergen (30) the readings were taken in the sitting

position, with the subject sitting on a chair with the arm placed horizontally on a table.

There is still some disagreement as to which of the two phases (phase IV or phase V) represents the true diastolic blood pressure.

Among the studies mentioned above Hamilton *et al.* (89) and Miall & Oldham (150, 151) employed muffling of the sounds prior to their disappearance as the diastolic blood pressure. In the study of Comstock (44) and in the mass investigation of Bergen (30) the point of disappearance (phase V) was used.

A comparison of indirect and direct measurements of arterial blood pressure shows somewhat different results. Ragan & Bordley (185) state, "The auscultatory measurements of diastolic pressure, employing sudden fading of the Korotkoff sounds as an index of diastolic pressure, were usually higher than the intra-arterial measurements. Hamilton, Woodbury & Harper (92) found the diastolic pressure to be increased by 9 mm when the fading of the fourth phase was used. Steele (220) also noted that the final cessation of sounds approximated to the directly estimated diastolic pressure more closely than did their sudden diminution in intensity. Similarly the Recommendations for Human Blood Pressure Determinations by Sphygmomanometers states, "The best index of diastolic pressure is the point of complete cessation of sounds. In the principles laid down by the American Heart Association in 1939 Standardiza-

tion of Blood Pressure Readings (219) it is recommended that the two values of the diastolic blood pressure should be recorded that is the point at which the sounds, suddenly become dull and muffled, if a difference exists between that point and the level at which the sounds completely disappear.

Burton (34) criticizes the use of the disappearance of the sounds as an index of the diastolic blood pressure and judges this from a physiological standpoint. Similarly Roberts, Smiley & Manning (197) conclude that, "The muffle bears a more constant and closer relationship to the 'true' diastolic pressure than does the disappearance of the sound. Van Bergen *et al.* (227) reach the same conclusions.

There is thus still some doubt as to which auscultatory phenomena are really valid for the diastolic blood pressure. However under most circumstances the authors agree that the indirect method measures the systolic and diastolic blood pressure with an accuracy sufficient for clinical studies.

The influence of arm size on the errors of indirect measurements has also been studied by Ragan & Bordley (185). The values of indirect measurements tended to be too low with small arms and too high with large arms. Pickering *et al.* (181) prepared a Table to show the corrections for arm circumference to be applied to auscultatory measurements. They concluded that the corrections are worth making where large groups of individuals are concerned. In single individuals the corrections are probably not worth applying since variations in arm circumference account for no more than a quarter of the differences between direct and indirect readings.

### The method of measurement in this study

Firstly it was important to measure the blood pressure in the same position and in the same way as in the mass investi-

gation in 1950 (see p. 29) to compare the blood pressure in that year to the measurements in 1951-52. A comparison between the blood pressure values over this time interval gives us some information of the variability of the systolic and the diastolic blood pressure and its relationship to the height of the blood pressure and age. It was of particular importance clinically to ascertain if any increase in blood pressure occurred, if there was any possibility of progression of the underlying illness, and in which age and blood pressure groups this occurred.

Next it was considered important to measure the blood pressure in a lying position, so that the subjects would have a better chance of relaxing and the physical and psychical stresses which always make themselves felt, could be reduced. It was clear that the individuals who were summoned by letter and asked to attend for a thorough clinical examination, would be more or less flurried, strained, and nervous. It was therefore of great importance to reduce these psychical stimuli. It was decided therefore to measure the blood pressure in the lying position and further to check the blood pressure after half an hour in the same position. The intervening time was spent on a general examination of the patient. The present state of health was recorded, and an ophthalmological examination was carried out. At the same time it was considered very important to reassure the patient.

The measurements in the lying position cannot be considered to be "basal" but more as resting blood pressures. It will therefore be of special interest to find the variation and the difference between the blood pressure values in the different position in relation to the age and the blood pressure.

The extent of the investigation, moreover made it impossible to take more measurements. It is of particular interest that this investigation, based on voluntary attendance, did not fall into disfavour with the public. Therefore from the very

beginning one gave up any idea of doing the more time-consuming tests, such as, for example Hines cold pressure test, Ayman and Goldhane's breath-holding test, or measurements under the influence of sedatives.

The measurement technique which has been used in this work was, like that used in 1950 based on criteria drawn up by the American Heart Association (see p. 29).

The systolic pressure was recorded at the sudden appearance of a clear sound (phase I). However the diastolic pressure was read at phase IV (sudden muffling of the sounds) in contrast to the mass investigation of Bergen, when phase V was used. The reason for this is that phase IV is considered to be somewhat more distinct than phase V and thus it can be determined more closely. Phase V is often difficult to determine as the sounds can be heard down to zero-level. This seems to be the case in the older age groups and especially in conditions associated with a water-hammer or Corrigan pulse. The decision as to when a sound ceases depends on how exactly and nicely one auscultates, and similarly the position of the stethoscope over the artery matters a great deal.

The measurements in the sitting position were taken with the arm abducted 45-60° and with the forearm resting on a table. The blood pressure cuff was placed on a level with the heart and the sphygmomanometer placed on the same table as the arm. In the lying position the arm was placed horizontally, abducted 30-45° and resting on a soft pad. The cuff was placed in such a way that the level was that of the mid-axillary line. The right arm was used as consistently as possible for all the measurements and only exceptionally when special conditions ruled this out was the left used.

In all positions three measurements were taken, the following other after a short pause. Care was taken to see that the cuff became completely deflated between each measurement to prevent con-

gestion of the blood distal to the cuff. The first measurement was taken mainly to get orientated and was taken relatively quickly; the next was taken slowly with precise observation of the quality of the sounds and the level of the column of mercury. The third measurement was taken in the same way and this value was recorded in the case sheet. During all these measurements the subjects were urged to rest and to relax.

The reason three measurements were taken is mainly based on the observations of Diehl & Lees (50). They concluded from a study of repeated measurements on 100 university freshmen that the mean of the first three readings of the series shows significant decreases between consecutive readings, but after the third reading the difference between any two consecutive readings is less than the probable error of the difference. The later report of Comstock (44) is also based on three readings repeated as soon as the examiners were certain that all the pressure in the cuff had been released.

The apparatus used for all the measurements was of the same construction and type, a mercury manometer standardised in advance, as in the mass investigation in 1950-51. The cuff was of standard type with a breadth of 13 cm, and this type of cuff was used on all individuals, irrespective of the thickness of the arm or the size of the subject. Corrections for arm circumference have not been applied in this study.

In order that the investigator should not be biased by the 1950 measurements, care was taken that the investigator had no knowledge of the exact blood pressure value that was found at the mass examination in the previous year. However it was not possible in most cases to escape the investigator knowing the systolic blood pressure group to which the subject belonged. However the diastolic blood pressure was in all cases completely unknown to the investigator. It was considered to be of a certain importance that the examiner should not be biased by the earlier meas-

urements, so that the comparisons between the values in 1950 and the measurements in 1951-52 should be as reliable as possible. The blood pressure values from the mass investigation in 1950 were not entered on the case sheets until after the end of the investigation.

### Accuracy of the blood pressure readings

The blood pressure was read to the nearest 0 or 5 value: more precise readings were considered to be of little worth. Abstracts from the literature show that Hamilton *et al.* (89) and Dhall & Oldham (150-151) recorded both the systolic and diastolic blood pressure to the nearest 5 mm Hg. Master *et al.* (143) Comstock (44) and Karpinos (110) recorded both pressures to the nearest digit.

The Bergen series shows that readings rounded off to values ending in 0 are much more frequent than values ending in 5. The proportion is about 6:1 and this has been discussed in more detail by Bøe, Humerfelt, & Wedervang (30 pp 48 and 103).

A survey of the literature gives some information on the accuracy of the readings considered in this manner. In the study of Master and his co-workers (143) the commonest terminal even digit was zero or eight, more often in the diastolic readings than in the systolic. They disregarded all reports where every reading

ended with zero since it was assumed that they were not accurate. Comstock (44) states that nearly all observers showed some tendency to record more readings ending in zero than in any other digit. It could be demonstrated that the higher the blood pressure reading the more marked the preference for a figure ending in zero. Karpinos (110) reports that 44 per cent of the systolic and 50 per cent of the diastolic blood pressures ended in 0 accompanied by a general preference for even numbers. Wetherby (231) also found an excess of readings to 0 values. Roberts, Smiley & Manning (192) have analysed the blood pressure readings taken by three doctors and found that the total number of readings ending in 0 or 5 'far exceeded the number that could be expected by chance. In spite of the fact that the investigation was carried out very conscientiously. These authors conclude that blood pressure measurements taken under the best conditions of investigation cannot be given more accurately than to the nearest 5 mm Hg even by an experienced investigator.

It must be emphasised that the 1950 Bergen series was recorded by 4 to 5 different investigators, while the present series was recorded solely by the author.

Table 6.1 gives the readings rounded off to values ending in 0 and 5 grouped according to the serial numbers.

The values obtained in the present series show a greater frequency of 0 than of 5 values, but the proportion of 0 to 5 read-

Table 6.1

| Serial Number | Systolic |       |                    | Diastolic |       |                    |
|---------------|----------|-------|--------------------|-----------|-------|--------------------|
|               | Sitting  | Lying | Resting 30 minutes | Sitting   | Lying | Resting 30 minutes |
| 1-499         | 2.3      | 2.0   | 1.9                | 3.6       | 2.3   | 2.3                |
| 500-999       | 2.1      | 2.3   | 2.0                | 3.0       | 2.3   | 2.8                |
| 1,000-1,550   | 2.7      | 2.5   | 2.3                | 4.1       | 3.5   | 3.5                |

The accuracy of the blood pressure readings. The figures indicate the ratio of the total numbers of readings to 0-values divided by the total number of readings to 5 according to serial numbers.

Table 6.2

| Blood pressure groups | Systolic                |     |       | Diastolic               |     |       |
|-----------------------|-------------------------|-----|-------|-------------------------|-----|-------|
|                       | Number of readings to 0 | 5   | ratio | Number of readings to 0 | 5   | ratio |
| Sitting               |                         |     |       |                         |     |       |
| ≥ 210                 | 173                     | 43  | 4.0   | 180                     | 36  | 5.0   |
| 180-205               | 257                     | 83  | 3.1   | 266                     | 74  | 3.6   |
| 150-175               | 430                     | 185 | 2.3   | 477                     | 158 | 3.0   |
| ≤ 145                 | 227                     | 152 | 1.5   | 287                     | 92  | 3.1   |
| Lying                 |                         |     |       |                         |     |       |
| ≥ 210                 | 167                     | 45  | 3.7   | 156                     | 56  | 2.8   |
| 180-205               | 234                     | 104 | 2.3   | 240                     | 98  | 2.4   |
| 150-175               | 415                     | 199 | 2.1   | 444                     | 170 | 2.6   |
| ≤ 145                 | 249                     | 129 | 1.9   | 276                     | 102 | 2.7   |
| Lying 30 minutes      |                         |     |       |                         |     |       |
| ≥ 210                 | 153                     | 53  | 2.9   | 151                     | 57  | 2.6   |
| 180-205               | 224                     | 111 | 2.0   | 238                     | 97  | 2.5   |
| 150-175               | 390                     | 223 | 1.7   | 461                     | 152 | 3.0   |
| ≤ 145                 | 263                     | 114 | 2.3   | 281                     | 96  | 2.9   |

The ratio of the blood pressure readings ending in 0 and 5 according to the height of the blood pressure in the different positions. The series is grouped into 4 blood pressure groups according to the systolic blood pressure in the sitting position 1951-52.

ings is much lower than in the 1950 Bergen series. Next one finds that the readings of the systolic blood pressure are quite consistent both in measurements in the different positions and on comparison of the measurements in the first 500 cases compared to the following groups. For the diastolic blood pressure, values ending in 0 are somewhat more common than with the systolic blood pressure. There is some difference in the diastolic readings in the different positions, and the last 550 cases show a greater frequency of 0 readings in all positions than the first 1 000.

When the series is grouped according to the blood pressure it is found that readings to 0 are relatively more common in the groups with high blood pressure. This is shown in Table 6.2.

The series is here grouped into 4 blood pressure groups, systolic in sitting position. While 0 readings for the systolic blood

pressure are four times more common in the highest blood pressure group, the ratio 0:5 falls off evenly to 1.5 in the lowest blood pressure group. The diastolic blood pressure gives similar findings in the corresponding groups, with the 0 readings 5 times more common in the highest and 3 times more common in the lowest group. This difference between 0 and 5 readings in the 4 blood pressure groups is considerably less marked in the systolic and completely eliminated in the diastolic blood pressure readings in the lying position. After 30 minutes rest in the lying position the difference in the readings in the high and low blood pressure groups is eliminated in both cases.

When the series is grouped into both blood pressure and age groups there is no particular difference to be seen in the 0 and 5 readings between the age groups. This applies to both blood pressures in all

three positions. (The Tables referring to these calculations have been omitted)

### Between observer variability Own readings in relation to other observers

In order to test the author's accuracy in reading the blood pressure the author took part in a group study of 5 observers measuring the blood pressure on 7 normal subjects and in a second study of 9 patients, suffering from varying degrees of hypertension and chronic bronchitis, also examined by five observers. The blood pressure was measured by each observer once only.

The blood pressure measurements were a part of an investigation organized by Holland (100) in order to determine observer variation in several physical methods. The investigation was arranged as a balanced Latin square experiment including 5 different physiological tests.

From these results it is shown that there is no significant difference between observers in reading the systolic or diastolic blood pressure according to phases IV and V.

### Discussion

In biological measurements it may happen that preference is shown for certain numbers. This is characteristic of for example the readings of the cutaneous tuberculin reaction. It has been demonstrated several times that different observers favour certain numbers. This has been seen in several epidemiological studies on blood pressure when the readings were taken by different observers.

Thus Comstock (44) states that all 4 observers preferred even digits and 0-values. Even in the blood pressure studies where the readings are recorded to the nearest 5 mm or 10 mm Hg below the observed figure a definite preference for 0-values is evident. This can be seen clearly from the mass investigation in Bergen (30) where 4-5 nurses took the measurements.

0-values were recorded in approximately 86 % and 5-digits in 14 %. Unfortunately each of the observers was not controlled, so the individual technique in taking the read gs cannot be evaluated. It is not apparent that any comparisons were made between the different observers in the investigations of Hamilton and co-workers (89).

In the present study readings to 0 were also found to be more common than readings to 5 digits. Even with measurements taken by the same person with the greatest possible precision, this has not been avoided. It was also to be expected that the investigator might tire as the study progressed, but in the case of the systolic blood pressure there is no definite difference in the 0-5 ratio for the first 500 serial numbers in comparison to the last. However the diastolic blood pressure shows an increase in the frequency of 0 readings in the last 550 serial numbers. It therefore cannot be excluded that the investigator really did tire as the investigation progressed. It is doubtful whether this factor can ever be avoided entirely in such extensive and time-consuming mass investigations.

A blood pressure measurement is a combined auditory and visual registration which calls for a certain amount of concentration. The danger in mass investigations is that one's concentration lessens as time passes, giving an increased tendency to round off the readings.

It has been shown previously that the relationship between 0 and 5 readings varies with the height of the blood pressure. Comstock (44) found that readings to values ending in 0 occurred in 29 % of the group with a systolic blood pressure under 140 mm and 38 % in the groups with a higher systolic blood pressure. The groups with a diastolic blood pressure under 100 mm showed 0 readings in 34 % and in groups with a higher diastolic blood pressure the figure was 60 %. Similar findings are to be seen in Master *et al*'s work (143) from 1952.



In the present study there is a considerable difference in the 0/5 ratio between the groups with high and those with low blood pressure measured in the sitting position. This applies to both the systolic and the diastolic blood pressure. We know that high blood pressures show a greater tendency to fluctuate than low blood pressures. It is not unlikely that this has some effect on the readings. It is surprising, however, that the difference in the 0/5 ratio between the groups with high and low blood pressure decreases in the lying position, and that this difference is more or less abolished when the measurements are taken after half an hour's rest. This applies to the systolic as well as to the diastolic blood pressure. It is not unlikely that the relaxation of muscular and nervous tension during rest reduces any fluctuations, so that it is easier to read the blood pressure exactly.

Study of the literature has shown that similar findings have not been reported previously.

## Summary and conclusion

The blood pressure was read to the nearest 0 or 5 value. The readings show a greater frequency of 0 than of 5 values, on average a 0/5 ratio of 2.3 for the systolic and of 3.5 for the diastolic blood pressure. On comparing the readings in the first 500 serial numbers to those following the readings of the systolic blood pressure are quite consistent in the different positions. However a greater frequency of 0 readings of the diastolic blood pressure was found in the last 550 numbers.

The 0 readings are more frequent in the groups with high blood pressure, giving a 0/5 ratio of 4.0 for the systolic and 5.0 for the diastolic decreasing to a 0/5 ratio of 1.5 for the systolic and 3.1 for the diastolic in the lowest blood pressure groups in the sitting position. When the subjects have rested for 30 minutes in the lying position this difference of the 0/5 ratio between the high and low blood pressure groups is eliminated both for the systolic and diastolic blood pressure.

## I The blood pressure distribution in 1950 and in 1951-52

### Introduction

The blood pressure distribution in this series, which has been divided into groups according to sex, age, and blood pressure, will be examined in the following pages. The method which has been chosen to analyse this series is illustrated in Fig. 6.1

In part *a* of this figure one sees the blood pressure distribution of one age group of the Bergen series. Part *b* shows this group broken up into subgroups on the basis of the level of the systolic blood pressure. Part *c* shows a stratification of the age group so that it can be studied as easily horizontally as vertically. The size of each group depends upon the percentage selection. Therefore the dimensions of the different groups will not be the same as in the original series.

In this way we get in all 24 groups (cells) of individuals of each sex, as the series is divided up into 6 age groups (15-29 30-39 40-49 50-59 60-69 and  $\geq 70$  years) and 4 blood pressure groups ( $\leq 145$  150-175 180-205  $\geq 210$  mm Hg) classified on the basis of the systolic blood pressure in 1950. Thus the groups in 1950 and 1951-52 contain the same individuals.

To give an over-all picture of the blood pressure in all these 24 groups (cells) we shall first examine the mean values and the variance in the different groups, and then we shall make comparisons between groups with the same age or with the same blood pressure.

The blood pressure distribution is represented in histograms. The distribution in 1950 is shown by a continuous line,

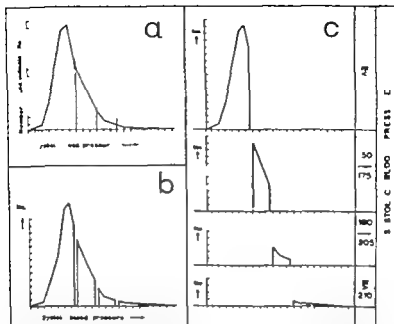


Fig 6.1 Blood pressure distribution curves. In part one sees one age group of the Bergen series. Part b shows this group broken up into sub-groups on the basis of the systolic blood pressure. Part c shows stratification of this age group.

while that for 1951-52 is shown by a broken line. In this case the histograms have been drawn in absolute values using the same scale with the total number of individuals as the ordinate and the blood pressure values as the abscissa. If one had chosen to represent the series in relative values with the total number of individuals given as percentage (the ordinate in the picture would be somewhat faulty. A group with few people would be given the same prominence as a group containing many people. The total number of individuals in each group has therefore been given in parentheses beside the histograms (see Fig 6.2). The mean values and the standard error of the mean are given on the right of the histogram, with the values for 1950 above, and the 1951-52 values below. Thus one can read directly from the different curves the numerical values of the blood pressure and at the same time

gain a real picture of the blood pressure distribution.

### The systolic blood pressure measured in the sitting position. The frequency distribution in 1950 and in 1951-52

The frequency distribution is shown in Fig 6.2 and Fig 6.3. The skewed blood pressure distribution in the 1950 groups is characteristic of both diagrams, as they represent different sub-groups. These groups are of small range, as the blood pressure values are limited to class interval of 30 mm Hg for the two central blood pressure groups (150-175 and 180-205) while the lowest and highest groups are open.

The mean values in 1950 (Table 6.3) show as was expected, fairly similar numerical values in the different age

In the present study there is a considerable difference in the 0/5 ratio between the groups with high and those with low blood pressure measured in the sitting position. This applies to both the systolic and the diastolic blood pressure. We know that high blood pressures show a greater tendency to fluctuate than low blood pressures. It is not unlikely that this has some effect on the readings. It is surprising, however, that the difference in the 0/5 ratio between the groups with high and low blood pressure decreases in the lying position, and that this difference is more or less abolished when the measurements are taken after half an hour's rest. This applies to the systolic as well as to the diastolic blood pressure. It is not unlikely that the relaxation of muscular and nervous tension during rest reduces any fluctuations, so that it is easier to read the blood pressure exactly.

Study of the literature has shown that similar findings have not been reported previously.

## Summary and conclusion

The blood pressure was read to the nearest 0 or 5 value. The readings show a greater frequency of 0 than of 5 values, on average a 0/5 ratio of 2.3 for the systolic and of 3.5 for the diastolic blood pressure. On comparing the readings in the first 500 serial numbers to those following the readings of the systolic blood pressure are quite consistent in the different positions. However a greater frequency of 0 readings of the diastolic blood pressure was found in the last 550 numbers.

The 0 readings are more frequent in the groups with high blood pressure, giving a 0/5 ratio of 4.0 for the systolic and 5.0 for the diastolic, decreasing to a 0/5 ratio of 1.5 for the systolic and 3.1 for the diastolic in the lowest blood pressure groups in the sitting position. When the subjects have rested for 30 minutes in the lying position this difference of the 0/5 ratio between the high and low blood pressure groups is eliminated both for the systolic and diastolic blood pressure.

## I The blood pressure distribution in 1950 and in 1951-52

### Introduction

The blood pressure distribution in this series, which has been divided into groups according to sex, age, and blood pressure, will be examined in the following pages. The method which has been chosen to analyse this series is illustrated in Fig. 61.

In part *a* of this figure one sees the blood pressure distribution of one age group of the Bergen series. Part *b* shows this group broken up into subgroups on the basis of the level of the systolic blood pressure. Part *c* shows a stratification of the age group so that it can be studied as easily horizontally as vertically. The size of each group depends upon the percentage selection. Therefore the dimensions of the different groups will not be the same as in the original series.

In this way we get in all 24 groups (cells) of individuals of each sex, as the series is divided up into 6 age groups (15-29 30-39 40-49 50-59 60-69 and  $\geq 70$  years) and 4 blood pressure groups ( $\leq 145$ , 150-175 180-205,  $\geq 210$  mm Hg) classified on the basis of the systolic blood pressure in 1950. Thus the groups in 1950 and 1951-52 contain the same individuals.

To give an over all picture of the blood pressure in all these 24 groups (cells) we shall first examine the mean values and the variance in the different groups, and then we shall make comparisons between groups with the same age or with the same blood pressure.

The blood pressure distribution is represented in histograms. The distribution in 1950 is shown by a continuous line,



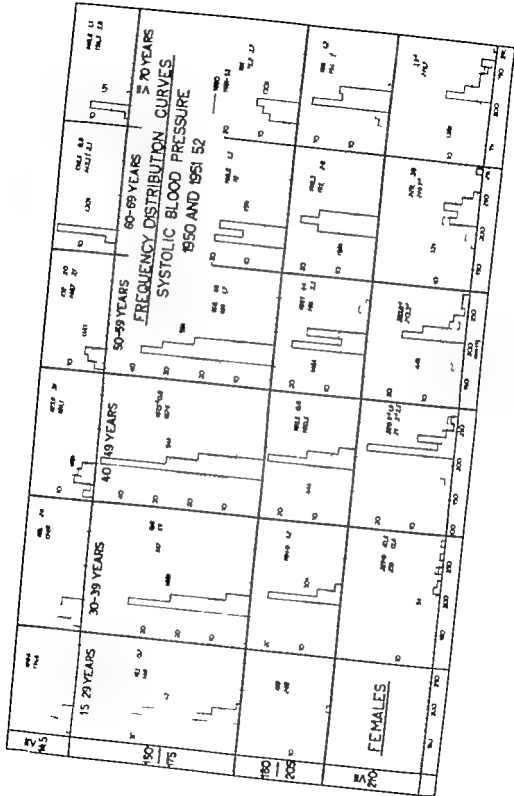


Table 6.4 *Systolic blood pressure in 1951/52 by age and sex*  
 Mean, standard error of the mean, standard deviation, and coefficient of variation

| BP groups 1950 |         | Age and sex groups |       |       |       |       |       |       |       |       |       |       |       |
|----------------|---------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                |         | 15-29              |       | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|                |         | M                  | F     | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| ≤ 145          | No.     | 19                 | 14    | 21    | 22    | 20    | 19    | 19    | 14    | 22    | 20    | 7     | 12    |
|                | Mean    | 123.4              | 124.6 | 128.3 | 134.8 | 135.3 | 136.1 | 136.8 | 145.7 | 143.6 | 147.3 | 148.6 | 156.3 |
|                | S. e.   | 2.5                | 3.1   | 2.4   | 2.7   | 1.9   | 3.1   | 3.0   | 3.1   | 3.3   | 2.3   | 9.2   | 3.8   |
|                | St. d.  | 10.5               | 11.2  | 10.9  | 12.3  | 8.2   | 13.2  | 12.9  | 11.3  | 15.2  | 9.8   | 22.6  | 19.0  |
|                | C. of v | 8.5                | 8.9   | 8.5   | 9.1   | 6.1   | 9.7   | 9.4   | 7.8   | 10.6  | 6.7   | 15.2  | 12.2  |
| 150-175        | No.     | 108                | 42    | 70    | 63    | 51    | 94    | 44    | 93    | 46    | 51    | 18    | 30    |
|                | Mean    | 147.9              | 149.9 | 145.6 | 147.3 | 152.6 | 157.6 | 153.8 | 159.9 | 171.9 | 172.4 | 163.1 | 175.2 |
|                | S. e.   | 1.1                | 2.1   | 1.5   | 1.9   | 2.0   | 1.4   | 3.0   | 1.7   | 4.0   | 3.1   | 5.0   | 3.7   |
|                | St. d.  | 11.0               | 13.9  | 12.3  | 15.2  | 14.4  | 13.7  | 19.6  | 16.4  | 26.5  | 22.2  | 20.6  | 19.9  |
|                | C. of v | 7.4                | 8.9   | 8.4   | 10.3  | 9.4   | 8.7   | 12.6  | 10.3  | 15.4  | 12.9  | 12.6  | 11.4  |
| 180-205        | No.     | 22                 | 1     | 40    | 30    | 32    | 44    | 21    | 45    | 33    | 56    | 22    | 51    |
|                | Mean    | 170.3              | 240   | 171.8 | 175.5 | 179.8 | 180.5 | 184.0 | 196.9 | 187.9 | 195.8 | 188.0 | 191.1 |
|                | S. e.   | 3.4                |       | 2.1   | 3.3   | 3.2   | 2.7   | 3.7   | 3.3   | 4.4   | 2.7   | 3.6   | 2.4   |
|                | St. d.  | 15.6               |       | 13.3  | 17.7  | 17.9  | 17.8  | 16.7  | 21.9  | 24.6  | 20.3  | 16.3  | 16.3  |
|                | C. of v | 9.1                |       | 7.7   | 10.1  | 10.0  | 9.9   | 9.1   | 11.1  | 13.1  | 10.5  | 8.7   | 8.4   |
| ≥ 210          | No.     |                    |       | 3     | 5     | 20    | 47    | 24    | 44    | 8     | 32    | 10    | 36    |
|                | Mean    |                    |       | 188.3 | 239.0 | 201.3 | 214.3 | 204.2 | 213.3 | 213.8 | 213.7 | 200.3 | 219.7 |
|                | S. e.   |                    |       | 13.9  | 13.6  | 4.3   | 3.5   | 5.6   | 4.3   | 4.8   | 3.9   | 9.4   | 4.3   |
|                | St. d.  |                    |       | 19.6  | 27.2  | 19.3  | 23.6  | 26.6  | 27.9  | 12.8  | 21.3  | 28.0  | 23.6  |
|                | C. of v |                    |       | 10.4  | 11.4  | 9.7   | 11.0  | 13.0  | 13.1  | 6.0   | 9.8   | 14.0  | 11.7  |

the groups with high blood pressure in 1950 particularly in the youngest age groups, and most pronounced in men. On the other hand there is an increase in the mean values in groups with low blood pressures in 1950. This increase is greatest in the older subjects and a little more pronounced in women (see page 78).

The range of the blood pressure values in each group expressed by the standard deviation and standard error of the mean, is considerable and undoubtedly greater at the 1951/52 measurements. This is illustrated by the frequency distribution curves. It shows up most distinctly in the higher blood pressure groups and is more prominent in the higher age groups.

a) *Analysis of the mean values of the groups*  
 Further analysis of these data bring some

other findings to light (cf. Fig. 6.4). It has been pointed out that the systolic blood pressure in 1951/52 sometimes showed a fall, and sometimes a rise in comparison to the 1950 values. This is shown more clearly in Fig. 6.4.

The distribution of the mean values gives a fairly uniform picture in the two sexes, as the mean values in 1951/52 show a fall in the youngest age groups in each of the three blood pressure groups over 150 mm Hg. However the lowest blood pressure group ( $\leq 145$ ) shows an increase in the mean values in all age groups except for the youngest male one. In the higher age groups the mean values in 1951/52 increased in all blood pressure groups except for the highest ( $\geq 210$ ). Thus a crossing of the mean values appears in the blood pressure groups 150-175 and

Table 6.2. Systolic blood pressures in 1950 by age and sex  
Mean, standard error of the mean, standard deviation, and coefficient of variation

| BP groups | 1950     | Age and sex groups |       |       |       |       |       |       |       |       |       |       |       |
|-----------|----------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|           |          | 15-29              |       | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|           |          | M                  | F     | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| ≤ 145     | No.      | 19                 | 14    | 21    | 22    | 20    | 19    | 19    | 14    | 22    | 20    | 7     | 12    |
|           | Mean     | 129.7              | 128.6 | 128.3 | 125.7 | 132.8 | 123.9 | 130.5 | 132.5 | 130.7 | 138.5 | 130.0 | 140.8 |
|           | S. e.    | 2.4                | 2.2   | 1.9   | 2.6   | 1.8   | 3.1   | 2.5   | 2.0   | 1.7   | 0.8   | 2.9   | 1.5   |
|           | St. d.   | 10.0               | 8.1   | 8.5   | 12.1  | 7.7   | 12.9  | 7.3   | 7.2   | 7.7   | 3.5   | 7.0   | 5.0   |
|           | C. of v. | 7.7                | 6.3   | 6.6   | 9.6   | 5.8   | 10.4  | 5.6   | 5.4   | 5.9   | 2.5   | 5.4   | 3.6   |
| 150-175   | No.      | 108                | 42    | 70    | 65    | 54    | 94    | 44    | 93    | 46    | 51    | 18    | 30    |
|           | Mean     | 155.8              | 153.0 | 157.2 | 155.8 | 158.4 | 157.5 | 158.3 | 158.9 | 159.8 | 160.6 | 159.2 | 161.7 |
|           | S. e.    | 0.7                | 0.7   | 1.0   | 0.8   | 1.0   | 0.8   | 1.7   | 0.8   | 1.0   | 1.0   | 1.8   | 1.5   |
|           | St. d.   | 7.6                | 4.2   | 8.0   | 6.2   | 7.6   | 8.0   | 7.9   | 7.5   | 9.2   | 7.1   | 7.3   | 6.9   |
|           | C. of v. | 4.9                | 2.7   | 5.1   | 4.0   | 4.8   | 5.1   | 5.0   | 4.7   | 5.8   | 4.4   | 4.6   | 4.5   |
| 180-205   | No.      | 22                 | 1     | 40    | 30    | 32    | 44    | 21    | 45    | 33    | 56    | 22    | 51    |
|           | Mean     | 184.1              | 180   | 183.8 | 184.0 | 188.6 | 185.5 | 184.3 | 189.1 | 185.9 | 190.3 | 185.0 | 188.9 |
|           | S. e.    | 1.4                |       | 0.8   | 1.2   | 1.3   | 0.8   | 1.2   | 1.4   | 1.4   | 1.0   | 1.6   | 1.2   |
|           | St. d.   | 6.5                |       | 4.7   | 6.5   | 7.2   | 5.5   | 6.1   | 9.3   | 7.6   | 7.6   | 7.2   | 8.6   |
|           | C. of v. | 3.5                |       | 2.6   | 3.5   | 3.9   | 3.0   | 3.3   | 4.9   | 4.1   | 4.0   | 3.9   | 4.6   |
| ≥ 210     | No.      |                    |       | 3     | 5     | 20    | 47    | 24    | 44    | 8     | 32    | 10    | 36    |
|           | Mean     |                    |       | 216.7 | 229.0 | 220   | 220.9 | 217.3 | 223.9 | 216.9 | 228.1 | 223.0 | 223.9 |
|           | S. e.    |                    |       | 6.1   | 10.5  | 2.7   | 1.9   | 2.4   | 2.6   | 2.5   | 3.0   | 5.0   | 3.4   |
|           | St. d.   |                    |       | 8.6   | 21.0  | 11.8  | 13.0  | 11.6  | 16.5  | 6.7   | 16.7  | 15.0  | 20.0  |
|           | C. of    |                    |       | 4.0   | 9.2   | 5.4   | 5.9   | 5.3   | 7.4   | 3.1   | 7.3   | 6.7   | 8.9   |

groups with the same blood pressure levels. One finds, however, a very slight increase in the values with age. Even if the groups are selected with the same class interval the tendency to increase in the mean systolic pressure with age is maintained slightly. This tendency is more marked in women. This seems natural as the increase in the blood pressure with age in the Bergen series of 1950 is plainly more marked in women. This is also evident from Fig. 6.4. The dispersion expressed by the standard deviation or standard error of the mean is rather similar for both sexes. The range is greatest in the highest blood pressure group and in this group greatest in women in all age groups, as expected from consideration of the primary series. The greatest range is seen in the age group

30-39 years in the blood pressure group ≥ 210 mm Hg. However the total number of individuals (5) is so low that the dispersion expressed by the standard error of the mean and the standard deviation must be great.

The blood pressure distribution in 1951/52 shows, in all groups and in both sexes, an almost symmetrical distribution. This is seen most clearly in the groups where the numbers are greatest. In solitary groups, however, one sees a tendency to a skewed distribution, as the curve becomes drawn out to the right (see the blood pressure group 180-205 for women). The mean values (Table 6.4) show somewhat different data in comparison to the 1950 values. This difference appears to be dependent on the blood pressure and on the age: there were lower mean values in

**Table 6.1** *Systolic blood pressure in 1951-52 by age and sex*  
Mean, standard error of the mean, standard deviation, and coefficient of variation

| BP groups | 1950     | Age and sex groups |       |       |       |       |       |       |       |       |       |       |       |
|-----------|----------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|           |          | 15-29              |       | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|           |          | M                  | F     | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| ≤ 145     | No.      | 19                 | 14    | 21    | 22    | 20    | 19    | 19    | 14    | 22    | 20    | 7     | 12    |
|           | Mean     | 123.4              | 131.6 | 128.3 | 134.8 | 133.3 | 136.1 | 136.8 | 143.7 | 143.6 | 147.3 | 148.6 | 156.3 |
|           | S. e.    | 2.5                | 3.1   | 2.4   | 2.7   | 1.9   | 3.1   | 3.0   | 3.1   | 3.3   | 2.3   | 9.2   | 3.8   |
|           | St. d.   | 10.5               | 11.2  | 10.9  | 12.3  | 8.2   | 13.2  | 12.9  | 11.3  | 15.2  | 9.8   | 22.6  | 19.0  |
|           | C. of v. | 8.5                | 8.5   | 8.5   | 9.1   | 6.1   | 9.7   | 9.4   | 7.8   | 10.6  | 6.7   | 15.2  | 12.2  |
| 150-175   | No.      | 108                | 42    | 70    | 65    | 54    | 94    | 44    | 93    | 46    | 51    | 18    | 30    |
|           | Mean     | 147.9              | 149.9 | 145.6 | 147.3 | 152.6 | 157.6 | 155.8 | 159.9 | 171.9 | 172.4 | 163.1 | 175.2 |
|           | S. e.    | 1.1                | 2.1   | 1.5   | 1.9   | 2.0   | 1.4   | 3.0   | 1.7   | 4.0   | 3.1   | 5.0   | 3.7   |
|           | St. d.   | 11.0               | 13.3  | 12.3  | 15.2  | 14.4  | 13.7  | 19.6  | 16.4  | 26.3  | 22.2  | 20.6  | 19.9  |
|           | C. of v. | 7.4                | 8.9   | 8.4   | 10.3  | 9.4   | 8.7   | 12.6  | 10.3  | 15.4  | 12.9  | 12.6  | 11.4  |
| 180-205   | No.      | 22                 | 1     | 40    | 30    | 32    | 44    | 21    | 45    | 33    | 56    | 22    | 51    |
|           | Mean     | 170.5              | 240   | 171.8 | 175.5 | 179.8 | 180.5 | 184.0 | 196.9 | 187.9 | 193.8 | 188.0 | 194.1 |
|           | S. e.    | 3.4                |       | 2.1   | 3.5   | 3.2   | 2.7   | 3.7   | 3.3   | 4.4   | 2.7   | 3.6   | 2.4   |
|           | St. d.   | 15.6               |       | 13.3  | 17.7  | 17.9  | 17.8  | 16.7  | 21.9  | 24.6  | 20.3  | 16.3  | 16.9  |
|           | C. of v. | 9.1                |       | 7.7   | 10.1  | 10.0  | 9.9   | 9.1   | 11.1  | 13.1  | 10.3  | 8.7   | 8.4   |
| ≥ 210     | No.      |                    |       | 3     | 5     | 20    | 47    | 24    | 44    | 8     | 32    | 10    | 36    |
|           | Mean     |                    |       | 188.3 | 239.0 | 201.3 | 214.3 | 204.2 | 213.3 | 213.8 | 219.7 | 200.3 | 19.7  |
|           | S. e.    |                    |       | 13.9  | 13.6  | 4.3   | 3.3   | 3.6   | 4.3   | 4.8   | 3.9   | 9.4   | 4.3   |
|           | St. d.   |                    |       | 19.6  | 27.2  | 19.3  | 23.6  | 26.6  | 27.9  | 12.8  | 21.5  | 28.0  | 23.6  |
|           | C. of v. |                    |       | 10.4  | 11.4  | 9.7   | 11.0  | 13.0  | 13.1  | 6.0   | 9.8   | 14.0  | 11.7  |

the groups with high blood pressure in 1950, particularly in the youngest age groups, and most pronounced in men. On the other hand there is an increase in the mean values in groups with low blood pressures in 1950. This increase is greatest in the older subjects and a little more pronounced in women (see page 78).

The range of the blood pressure values in each group expressed by the standard deviation and standard error of the mean, is considerable and undoubtedly greater at the 1951-52 measurements. This is illustrated by the frequency distribution curves. It shows up most distinctly in the higher blood pressure groups and is more prominent in the higher age groups.

a) *Analysis of the mean values of the groups*  
Further analyses of these data bring some

other findings to light (cf Fig 6.4). It has been pointed out that the systolic blood pressure in 1951-52 sometimes showed a fall, and sometimes a rise in comparison to the 1950 values. This is shown more clearly in Fig 6.4.

The distribution of the mean values gives a fairly uniform picture in the two sexes, as the mean values in 1951-52 show a fall in the youngest age groups in each of the three blood pressure groups over 150 mm Hg. However the lowest blood pressure group ( $\leq 145$ ) shows an increase in the mean values in all age groups except for the youngest male one. In the higher age groups the mean values in 1951-52 increased in all blood pressure groups except for the highest ( $\geq 210$ ). Thus a crossing of the mean values appears in the blood pressure groups 150-175 and



## SYSTOLIC BLOOD PRESSURE 1950 AND 1951-52

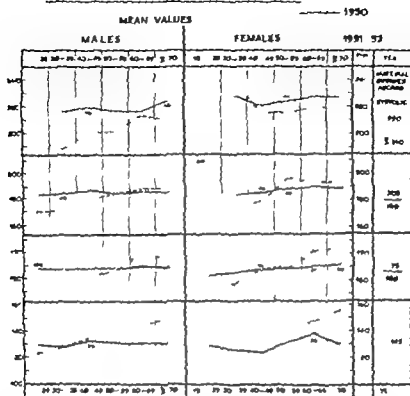


Fig. 6.4 The mean values of the systolic blood pressure in 1950 and in 1951-52 are shown for each of the four blood pressure groups, divided according to age and sex. The material is grouped by the systolic blood pressure in 1950.

180-205 mm Hg in men after 50-59 years of age and in women somewhat earlier.

If one considers this change in the mean systolic blood pressure in relation to the primary series a characteristic trend appears, see Fig. 6.5.

This Figure shows that in the groups with a low systolic blood pressure ( $\leq 145$  mm Hg) the mean values of the groups in 1951-52 show a rise, and this rise is greatest in the highest age groups. In the blood pressure groups 150-175 and 180-205 mm Hg we find a fall in the younger an entirely insignificant difference in the middle, and a rise in the highest age group.

In the highest blood pressure groups

( $\geq 210$  mm Hg) one finds a fall in almost all blood pressure groups; this is greatest among the young and as mentioned earlier more marked in men. An exception to this rule is shown by the women's group composed of one individual in the 15-29 age group and 5 individuals in the 30-39 age group.

This tendency of the mean systolic blood pressure appears to be fairly interesting when applying this to the findings from the blood pressure measurement of group I of the Bergen series (cp. B6e, Humbert, & Wedervang 30 pp. 74 and 75 Figs. 3a and 3b). One finds that the mean values in 1951-52 tend to be closer to the median, so that the scatter becomes

DIFFERENCE OF MEAN  
SYSTOLIC BLOOD PRES-  
SURE 1950 & 1951 1952  
ACCORDING TO AGE  
AND B.P. GROUPS

MALES ————  
FEMALES - - - - -

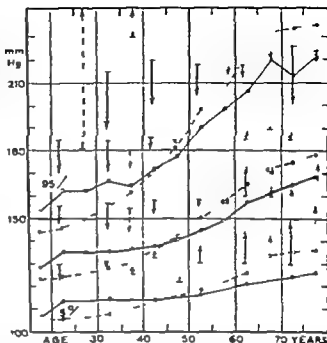


Fig 6.5. The differences between the mean values in 1950 and in 1951-52 are illustrated by arrows superimposed upon the distribution curves from the mass-investigation 1950 giving the median, 5% and 95% values. The direction of the arrows indicates either rise or fall in the mean values. The bases of the arrows give the mean values in 1950 and the points of the arrows the mean values in 1951-52.

less. The difference between the group averages is greatest in the groups which lie furthest from the median on the diagram. However the groups in which the average pressure lies near to the median show an insignificant difference. This applies in both sexes with the exception of the 6 women mentioned above.

b) *The difference between the systolic blood pressure in 1950 and in 1951-52*

We have up to now considered the mean values and the distribution of the systolic blood pressure, measured in a sitting position, in each of the 24 groups in the two sexes. But we know little of the blood pressure variation in every single individual in each of these groups.

To clarify this the difference between the systolic blood pressure in each indi-

vidual has been calculated in all 24 groups in the two sexes (Table 6.5). The calculations have been done in such a way that the 1951-52 values have been subtracted from the 1950 values. A negative difference signifies increase in the blood pressure and a positive difference a fall in the blood pressure in 1951-52. These differences are presented as frequency distribution curves, see Figs. 6.6 & 6.7.

The groups show an almost symmetrical distribution of the blood pressure differences. In many groups the range of the differences, as seen from the histograms, is quite large.

There is a tendency to an increase in range with rising blood pressure in women. This is not evident in men, as the numbers are too small in the groups with a systolic blood pressure of  $\geq 210$  mm Hg. Within

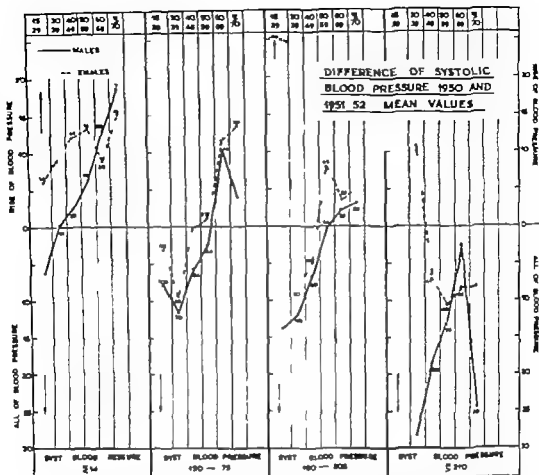


Fig. 6.8. The mean values of the blood pressure differences are arranged in 4 blood pressure groups, classified on the basis of the systolic blood pressure in 1950. Each of the 4 blood pressure groups is divided into 6 age groups. The diagram illustrates the rise or fall in the mean values relative to the 1950 values, which are represented by the zero-line.

In addition the eldest male group (10 individuals) with blood pressures  $\geq 210$  mm shows a marked fall in the blood pressure.

It should be mentioned that this more or less linear course of the mean values could apply only to this series. The class-intervals in the groups have been chosen arbitrarily. If the material was to be grouped on the basis of other blood pressures these lines would have followed a different course. Therefore it is of little purpose to subject the material to an exhaustive statistical analysis.

### Summary and conclusion

The blood pressure distribution is presented as histograms for each of the 24 groups (cells) in both sexes.

The frequency distribution curves of the systolic blood pressure in the 1950 groups are skew in both sexes, due to the stratification of the material. The distribution in 1951-52, on the other hand, is almost symmetrical. The mean values in 1950 show a very slight increase with age that is more marked in the women. The range is greatest in the highest blood pressure groups,

especially among women. The *mean values* in 1951-52 are lower in the groups that had high blood pressure in 1950. On the other hand there is an increase in groups with low blood pressures in 1950. The range is considerable and greater in 1951-52 than in 1950 (see Fig. 6.4).

The *difference between the mean values* in 1950 and 1951-52 shows a characteristic trend when superimposed upon the distribution curves from the mass investigation in 1950 (see Fig. 6.5).

The differences in the systolic blood pressure between the first reading in 1950 and the second in 1951-52, in both sexes, in *every individual* in each of the 24 cells, show a characteristic regularity when treated collectively.

The blood pressure tends to increase in the groups where the values were low ( $\leq 145$  mm Hg) in 1950 and this increase is most pronounced in the higher age groups. In the higher blood pressure groups (150-175 and 180-205 mm Hg) there is, however, a decrease in the younger and an increase in the older age groups. In the highest blood pressure group ( $\geq 210$  mm Hg) there is a fall of the blood pressure in all age groups, except for one group of women. Thus the *mean values of the differences* vary according to the blood pressure and follow an almost linear course with increasing age (see Fig. 6.8). There is, however, an exception among young women and among the oldest men in the highest blood pressure group.

Table 6.6. *Diastolic blood pressure in 1950 by age and sex*  
Mean, standard error of the mean, standard deviation, and coefficient of variation

| BP groups  |          | Age and sex groups |      |       |       |       |       |       |       |       |       |           |       |
|------------|----------|--------------------|------|-------|-------|-------|-------|-------|-------|-------|-------|-----------|-------|
|            |          | 15-29              |      | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | $\geq 70$ |       |
|            |          | M                  | F    | M     | F     | M     | F     | M     | F     | M     | F     | M         | F     |
| 1950       | No.      | 19                 | 14   | 21    | 22    | 20    | 19    | 19    | 14    | 22    | 20    | 7         | 12    |
|            | Mean     | 74.5               | 72.5 | 74.1  | 73.0  | 84.8  | 74.2  | 78.4  | 76.1  | 75.5  | 80.8  | 78.6      | 74.2  |
|            | S. e.    | 2.5                | 2.6  | 2.5   | 1.9   | 1.5   | 2.4   | 2.1   | 2.3   | 2     | 2.5   | 3.9       | 2.4   |
|            | St. d.   | 9.6                | 9.4  | 10.5  | 8.6   | 6.7   | 8.1   | 9.0   | 8.2   | 9.1   | 9.9   | 9.6       | 8.1   |
|            | C. of v. | 12.9               | 13.0 | 14.2  | 11.7  | 7.9   | 10.9  | 11.5  | 10.8  | 12.1  | 12.5  | 12.2      | 10.9  |
| 150-175    | No.      | 108                | 42   | 70    | 65    | 54    | 94    | 44    | 95    | 46    | 51    | 18        | 30    |
|            | Mean     | 83.5               | 82.5 | 89.5  | 87.8  | 91.6  | 89.6  | 87.4  | 89.4  | 89.7  | 86.5  | 84.2      | 87.2  |
|            | S. e.    | 1.1                | 1.5  | 1.2   | 1.2   | 1.1   | 0.8   | 1.7   | 0.9   | 1.5   | 1.3   | 2.4       | 1.6   |
|            | St. d.   | 11.0               | 9.8  | 9.9   | 9.6   | 7.7   | 8.1   | 10.9  | 8.7   | 10.0  | 9.0   | 10.0      | 8.9   |
|            | C. of v. | 13.2               | 11.9 | 11.1  | 10.9  | 8.4   | 9.0   | 12.5  | 9.7   | 11.1  | 10.4  | 11.9      | 10.2  |
| 180-205    | No.      | 22                 | 1    | 40    | 30    | 32    | 44    | 21    | 45    | 33    | 56    | 22        | 51    |
|            | Mean     | 92.3               | 100  | 95.0  | 94.7  | 101.3 | 99.2  | 102.6 | 99.6  | 96.5  | 97.9  | 91.1      | 91.8  |
|            | S. e.    | 5                  |      | 1.9   | 2.2   | 3.7   | 1.4   | 2.5   | 1.9   | 2.0   | 1.3   | 1.7       | 1.2   |
|            | St. d.   | 15.6               |      | 11.7  | 11.8  | 20.4  | 9.1   | 11.3  | 12.5  | 11.8  | 9.6   | 7.9       | 8.1   |
|            | C. of v. | 14.7               |      | 12.3  | 12.5  | 20.1  | 9.2   | 11.0  | 12.5  | 12.2  | 9.8   | 8.7       | 8.8   |
| $\geq 210$ | No.      |                    |      | 3     | 5     | 20    | 47    | 24    | 44    | 8     | 32    | 10        | 36    |
|            | Mean     |                    |      | 123.3 | 119.0 | 102.3 | 115.9 | 115.0 | 116.1 | 108.1 | 108.3 | 105       | 109.4 |
|            | S. e.    |                    |      | 14.7  | 8     | 6.9   | 2.4   | 3.8   | 2.4   | 7.4   | 2.7   | 3.7       | 2.3   |
|            | St. d.   |                    |      | 20.7  | 15.9  | 30.2  | 15.9  | 18.6  | 15.5  | 19.4  | 14.8  | 11.1      | 13.8  |
|            | C. of v. |                    |      | 16.8  | 13.4  | 29.5  | 13.7  | 16.2  | 13.4  | 17.9  | 13.7  | 10.6      | 12.6  |

Table 6.7 Diastolic blood pressure in 1951-52 by age and sex  
Mean, standard error of the mean, standard deviation, and coefficient of variation

| BP groups | 1950     | Age and sex groups |      |       |       |       |       |       |       |       |       |       |       |
|-----------|----------|--------------------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|           |          | 15-29              |      | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|           |          | M                  | F    | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| ≤ 145     | No.      | 19                 | 14   | 21    | 22    | 20    | 19    | 19    | 14    | 22    | 20    | 7     | 12    |
|           | Mean     | 75.3               | 83.2 | 79.8  | 84.1  | 85.5  | 84.7  | 85    | 88.6  | 86.1  | 91.0  | 83.6  | 84.2  |
|           | S. e.    | 1.3                | 2.0  | 1.4   | 1.9   | 1.8   | 1.8   | 2.0   | 2.2   | 2.1   | 1.4   | 2.7   | 2.4   |
|           | St. d.   | 5.7                | 7.3  | 6.3   | 8.9   | 8.0   | 7.7   | 8.5   | 8.0   | 9.8   | 6.0   | 6.5   | 8.0   |
|           | C. of v. | 7.6                | 8.8  | 7.9   | 10.6  | 9.4   | 9.1   | 10.0  | 9.0   | 11.4  | 6.6   | 7.8   | 9.5   |
| 150-175   | No.      | 108                | 42   | 70    | 65    | 54    | 94    | 44    | 93    | 46    | 51    | 18    | 30    |
|           | Mean     | 90.6               | 92.6 | 92.4  | 92.2  | 96    | 93.6  | 93.8  | 94.4  | 99.7  | 98.6  | 95.3  | 94.8  |
|           | S. e.    | 0.7                | 1.0  | 0.9   | 1.3   | 1.2   | 0.8   | 1.5   | 0.9   | 2.2   | 0.8   | 2.4   | 2.1   |
|           | St. d.   | 6.7                | 6.2  | 7.4   | 10.3  | 8.8   | 7.7   | 9.6   | 8.7   | 14.5  | 5.7   | 9.7   | 11.3  |
|           | C. of v. | 7.4                | 6.7  | 8.0   | 11.2  | 9.2   | 8.1   | 10.2  | 9.2   | 14.5  | 5.8   | 10.1  | 11.9  |
| 180-205   | No.      | 22                 | 1    | 40    | 30    | 32    | 44    | 21    | 45    | 33    | 56    | 22    | 51    |
|           | Mean     | 94.1               | 140  | 97.4  | 103.2 | 105.6 | 105.6 | 107.6 | 109.9 | 103.6 | 107.7 | 103.6 | 102.4 |
|           | S. e.    | 1.8                |      | 1.9   | 2.2   | 2     | 1.3   | 2.3   | 1.8   | 2.3   | 1.5   | 2.1   | 1.4   |
|           | St. d.   | 8.4                |      | 11.8  | 11.6  | 10.9  | 8.7   | 10.5  | 11.9  | 13.0  | 11.2  | 9.7   | 10.1  |
|           | C. of v. | 8.9                |      | 12.1  | 11.2  | 10.2  | 8.2   | 9.8   | 10.8  | 12.5  | 10.4  | 9.4   | 9.9   |
| ≥ 210     | No.      |                    |      | 3     | 5     | 20    | 47    | 24    | 44    | 8     | 32    | 10    | 36    |
|           | Mean     |                    |      | 116.7 | 130.0 | 109.5 | 119.1 | 115.4 | 117.8 | 111.3 | 116.6 | 107.5 | 115.0 |
|           | S. e.    |                    |      | 16.5  | 5.5   | 6.1   | 2.2   | 4.0   | 2.2   | 6.9   | 2.7   | 4.4   | 2.3   |
|           | St. d.   |                    |      | 23.4  | 10.9  | 26.5  | 14.8  | 19.2  | 14.5  | 18.1  | 15.2  | 13.0  | 13.3  |
|           | C. of v. |                    |      | 20.1  | 8.4   | 24.2  | 12.4  | 16.6  | 12.5  | 16.3  | 13.0  | 12.1  | 11.6  |

The diastolic blood pressure, measured in the sitting position in 1950 and in 1951-52

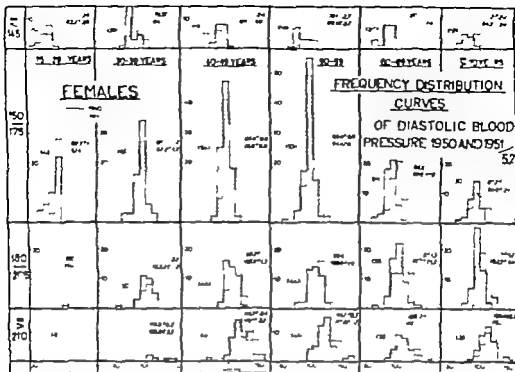
In the following pages we shall consider the diastolic blood pressure of the same groups. The groups are selected on the basis of classification by systolic pressure and each group is composed of the same individuals that were used in the study of the systolic blood pressure. The grouping and the stratification are the same, and the method of analysis will follow the same lines.

The frequency distribution of the diastolic blood pressure is shown in Fig. 6.9 (females) and Fig. 6.10 (males).

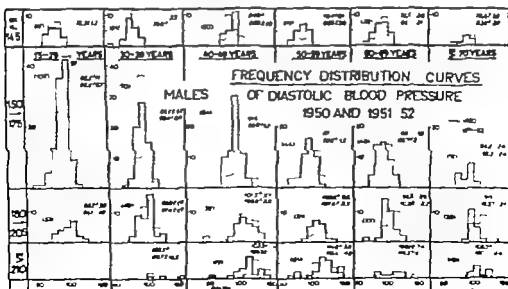
In contrast to the distribution of the systolic blood pressure in 1950 (Figs. 6.2 and 6.3) the diastolic blood pressure ap-

pears to be fairly symmetrically distributed both in 1950 and in 1951-52. A selection of the material on the basis of the systolic blood pressure does not lead to any essential skewness in the distribution of the diastolic blood pressure.

The dispersion within comparable groups, expressed by the standard deviation or the standard error of the mean (Table 6.6) is nearly the same for both sexes. Neither is there any great difference in the range of the measurements taken in 1950 and 1951-52. There appears to be no increase in the range with age in the same blood pressure group. On the other hand, there is some increase with higher blood pressure within the same age groups. Thus also appears from the shape of the frequency distribution curves and holds for both measurements.



Figs. 6.9 & 6.10. The histograms show the frequency distribution curves of the diastolic blood pressure 1950 (continuous lines) and 1951 52 (broken lines). Points of reference are given in detail in Figures 6.2 & 6.3. A selection of the material on the basis of the systolic blood pressure does not lead to any essential skewness in the distribution of the diastolic blood pressure. The mean values in 1951 52 are consistently higher than the 1950 values. This difference is due mainly to the different techniques used.



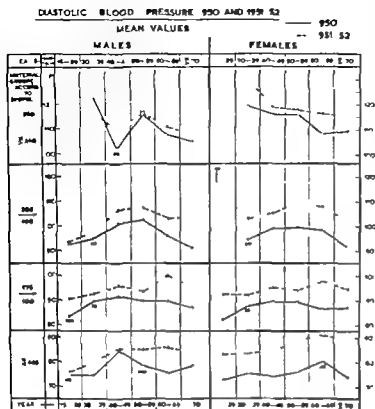


Fig 6.11 The mean values of the diastolic blood pressure in 1950 and in 1951-52 are shown for each of the four blood pressure groups, divided according to age and sex. The series is grouped according to the systolic blood pressure in 1950. The Figure shows the higher mean values of the diastolic blood pressure at the 1951-52 readings.

The mean values in 1950 prove to be relatively constant in the same blood pressure group without the tendency to increase with age that was found with the systolic blood pressure. However there is a decrease in the mean diastolic blood pressure in the highest age groups. This holds for nearly all blood pressure groups in both sexes.

The Bergen series (group I) also shows a fall in the diastolic blood pressure in the highest age groups.

The mean values in 1951-52 (Table 6.7) are consistently higher than the 1950 values. This applies to all groups of both sexes, with the exception of the group of three men of 30-39 years in the group systolic  $\geq 210$  mm Hg.

a) *Analysis of the mean values of the groups*  
To illustrate the difference between the 1950 and 1951-52 measurements more clearly the mean values of the two read-

ings have been recorded on a diagram, in the same manner as that used in Fig 6.4

From this it appears that the mean values are consistently higher in the 1951-52 readings. The differences between the mean values are relatively constant for the women in each blood pressure group, with the exception of the two younger groups mentioned before, in which the difference is great (see p. 76). In the men the differences seem to show a slight increase with age in the three lower blood pressure groups. The highest group shows somewhat varying values.

This difference in the mean values is due mainly to the different techniques used. The diastolic reading at the time of the first study was taken at phase V while on the second occasion it was taken at phase IV. A closer account of this has been given earlier (p. 66).

Table 6.8. The difference between the diastolic blood pressure in 1950 and in 1951/52 by age and sex  
Mean, standard error of the mean, and standard deviation

| BP groups | 1950   | Age and sex groups |       |       |       |       |       |       |       |       |       |       |       |
|-----------|--------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|           |        | 15-29              |       | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|           |        | M                  | F     | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| ≤ 145     | No.    | 19                 | 14    | 21    | 22    | 20    | 19    | 19    | 14    | 22    | 20    | 7     | 12    |
|           | Mean   | -0.8               | -10.7 | -5.7  | -9.1  | -0.8  | -10.5 | -6.6  | -12.5 | -10.7 | -10.3 | -5.0  | -10.0 |
|           | S. e.  | 2.4                | 2.9   | 2.5   | 2.2   | 2.0   | 2.2   | 2.8   | 3.5   | 2.1   | 2.2   | 2.4   | 2.6   |
|           | St. d. | 10.1               | 10.3  | 11.4  | 9.8   | 8.8   | 9.1   | 12.0  | 11.7  | 9.4   | 9.7   | 5.9   | 8.6   |
| 150-175   | No.    | 108                | 42    | 70    | 65    | 54    | 94    | 44    | 93    | 46    | 51    | 18    | 50    |
|           | Mean   | -7.1               | -10.4 | -2.9  | -4.5  | -4.4  | -6.0  | -6.4  | -5.0  | -10.0 | -12.2 | -11.1 | -7.7  |
|           | S. e.  | 1.1                | 1.7   | 1.1   | 1.5   | 1.4   | 0.9   | 2.0   | 1.0   | 1.9   | 1.8   | 3.2   | 2.4   |
|           | St. d. | 11.6               | 11.1  | 8.9   | 10.4  | 10.7  | 8.7   | 15.5  | 9.6   | 12.9  | 12.6  | 13.4  | 12.8  |
| 180-205   | No.    | 22                 | 1     | 40    | 30    | 32    | 44    | 21    | 45    | 33    | 56    | 22    | 51    |
|           | Mean   | -1.5               | -40.0 | -2.4  | -8.5  | -5.5  | -6.4  | -5.0  | -10.5 | -6.7  | -9.8  | -12.5 | -10.2 |
|           | S. e.  | 3.5                |       | 1.9   | 2.1   | 2.5   | 1.6   | 2.1   | 1.9   | 1.8   | 1.7   | 2.2   | 1.4   |
|           | St. d. | 15.1               |       | 11.6  | 11.1  | 13.9  | 10.6  | 9.2   | 12.8  | 12.2  | 12.9  | 10.2  | 10.2  |
| ≥ 210     | No.    |                    |       | 3     | 5     | 20    | 47    | 24    | 44    | 8     | 37    | 10    | 36    |
|           | Mean   |                    |       | -6.7  | -11.0 | -7.5  | -3.5  | -0.6  | -1.7  | -3.1  | -8.5  | -2.5  | -5.6  |
|           | S. e.  |                    |       | 6.6   | 7.0   | 3.0   | 2.1   | 5.6   | 2.5   | 2.5   |       | 3.5   | 2.3   |
|           | St. d. |                    |       | 9.4   | 13.9  | 13.1  | 14.5  | 17.1  | 15.1  | 8.1   |       | 10.5  | 13.3  |

Since the measurements were taken by different methods, it is of little use to work further on these findings.

b) The difference between the diastolic blood pressure in 1950 and in 1951/52

The difference between the diastolic blood pressures in every single individual in all the 24 groups in both sexes has been calculated by the same method as that used for the systolic blood pressure. The calculations have also been made in such a way that the 1951/52 values have been subtracted from the 1950 values. A negative difference signifies increase in the diastolic blood pressure and a positive difference a fall in the blood pressure. The differences are presented as frequency distribution curves for both sexes. The histograms have been drawn up in the same way as has been described for the systolic blood pressure (see Fig. 6.6)

The frequency distribution of the dif-

ferences is illustrated in Fig. 6.12 (females) and Fig. 6.13 (males). The groups do not always show the same symmetrical distribution above and below the zero-line as the differences between the systolic blood pressures. The variations in both positive and negative differences are not of the same magnitude. Many groups show a skewed distribution towards the left (towards the negative values)

The range of the differences (Table 6.8) appears to increase a little in the higher blood pressure group of the same age. However the tendency to increased range with age within the same blood pressure group as described for the systolic blood pressure, is not seen.

The mean values of these differences also show an increase from 1950 to 1951/52.

If one analyses all the positive and negative differences and relates the findings to the measurements in 1950 one gets the following diagram, see Fig. 6.14



## DIASTOLIC BLOOD PRESSURE 1950 AND 1951-52

## MEAN VALUES

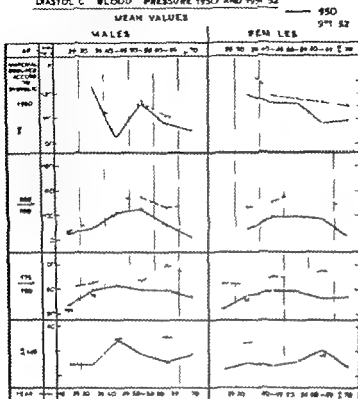


Fig 6.11 The mean values of the diastolic blood pressure in 1950 and in 1951-52 are shown for each of the four blood pressure groups, divided according to age and sex. The series is grouped according to the systolic blood pressure in 1950. The Figure shows the higher mean values of the diastolic blood pressure at the 1951-52 readings.

The mean values in 1950 prove to be relatively constant in the same blood pressure group, without the tendency to increase with age that was found with the systolic blood pressure. However there is a decrease in the mean diastolic blood pressure in the highest age groups. This holds for nearly all blood pressure groups in both sexes.

The Bergen series (group I) also shows a fall in the diastolic blood pressure in the highest age groups.

The mean values in 1951-52 (Table 6.7) are consistently higher than the 1950 values. This applies to all groups of both sexes with the exception of the group of three men of 30-39 years in the group systolic  $\geq 210$  mm Hg.

a) Analysis of the mean values of the groups To illustrate the difference between the 1950 and 1951-52 measurements more clearly the mean values of the two read-

ings have been recorded on a diagram, in the same manner as that used in Fig 6.4

From this it appears that the mean values are consistently higher in the 1951-52 readings. The differences between the mean values are relatively constant for the women in each blood pressure group, with the exception of the two younger groups mentioned before, in which the difference is great (see p. 76). In the men the differences seem to show a slight increase with age in the three lower blood pressure groups. The highest group shows somewhat varying values.

This difference in the mean values is due mainly to the different techniques used. The diastolic reading at the time of the first study was taken at phase V while on the second occasion it was taken at phase IV. A closer account of this has been given earlier (p. 66).

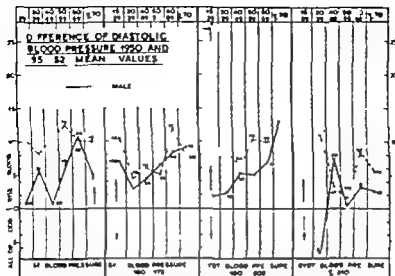


Fig. 6.14 The Figure shows the mean rise or fall in the diastolic blood pressure for the groups according to the height or their original pressures. Points of reference are given in detail in Figure 6.8. The average values of the differences for the women are generally higher than those for the men. The differences for the men show a tendency to increase with increasing age in the three lower blood pressure groups.

The mean values of the differences are grouped in the same manner as in Fig. 6.8. The 1950 values are represented by the zero-line.

In both sexes one finds higher diastolic values in the 1951-52 measurements. The calculations of the mean diastolic blood pressure (Fig. 6.11) showed the same, but this diagram illustrates the sex difference clearly. The average values of the differences for the women are generally higher than those for the men. The differences for the men show a tendency to increase with increasing age in the blood pressure groups  $\leq 145$ , 150-175 and 180-205 mm. This increase with age is not seen among the women.

### Summary and conclusion

The method of analysis of the diastolic blood pressure follows the same lines as those used for the systolic.

The frequency distribution of the diastolic pressure is nearly symmetrical, both in 1950 and in 1951-52. The mean values in 1951-52 are invariably higher than the 1950 values in all 24 cells in both sexes, with the exception of one group. This difference is mainly due to the different techniques used in taking the blood pressure.

When calculating the mean values of the differences between the 1950 and the 1951-52 readings in every single individual

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Fig. 6.12 & 6.13. The histograms show the difference between the diastolic blood pressure in 1950 and in 1951-52. Points of reference are given in detail in Figures 6.6 & 6.7. The mean values do not always show the same symmetrical distribution above and below the zero-line as the systolic pressure. The mean values of the differences show an increase from 1950 to 1951-52, mainly due to the different techniques used in taking the blood pressure.

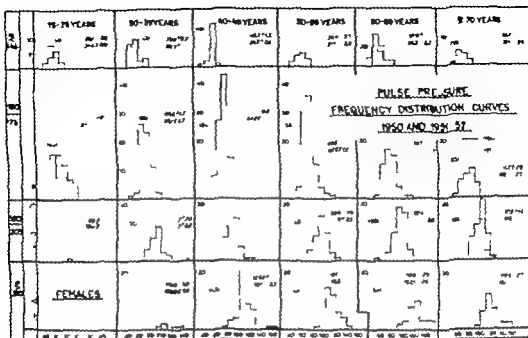
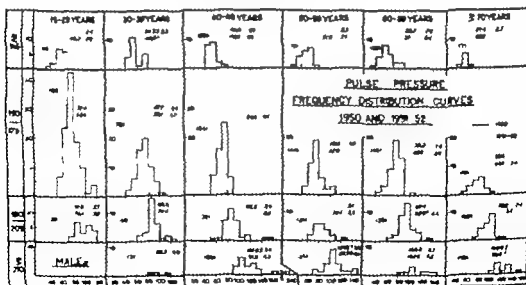


Fig. 6.15 & 6.16. Points of reference are given in detail in Figures 6.2 & 6.3. The frequency distribution of the 1950 values is more symmetrical than that of the systolic blood pressure, but in many of the groups the distribution is irregular. There is a distinct increase in the pulse pressure with rising blood pressure in the same age group in both sexes. The mean values of the 1951-52 measurements are on the whole lower due to the combination of lower systolic and higher diastolic blood pressures.



one finds that the mean values of the differences for the women are, with few exceptions, higher than those for the men.

### The pulse pressure in 1950 and in 1951-52

Analysis of the pulse pressure follows the same lines described for the systolic and diastolic blood pressures (see pp 70 and 82)

The frequency distribution of the pulse pressure is presented in Fig 6.15 (females) and Fig 6.16 (males)

The frequency distribution of the 1950 values is more symmetrical than that of the systolic blood pressure, but in many of the groups the distribution is irregular. The grouping of the material is based on the systolic blood pressure without any

regard being paid to the diastolic. It follows that the pulse pressure shows variations, and the curves illustrate this.

The mean values for the pulse pressure in 1950 in both the sexes are fairly similar in groups with the same blood pressure. In women there is a slight increase with age in all blood pressure groups, as was found for the systolic blood pressure. This is only seen in the highest blood pressure group in men.

As expected there is a distinct increase of the pulse pressure with rising blood pressure in the same age group in both sexes.

The dispersion expressed by the standard deviation or the standard error of the mean (Tables 6.9 and 6.10) does not show any real difference in comparable groups in the two sexes, neither is there any

Table 6.9 The pulse pressure in 1950 by age and sex  
Mean, standard error of the mean, standard deviation, and coefficient of variation

| BP groups |         | Age and sex groups |      |       |       |       |       |       |       |       |       |       |       |
|-----------|---------|--------------------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|           |         | 15-29              |      | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|           |         | M                  | F    | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| 1950      | No.     | 19                 | 14   | 21    | 22    | 20    | 19    | 19    | 14    | 22    | 20    | 7     | 12    |
|           | Mean    | 55.3               | 56.1 | 54.3  | 50.7  | 48    | 49.7  | 51.2  | 56.4  | 53.2  | 57.8  | 51.4  | 66.7  |
|           | S. e.   | 2.4                | 2.5  | 2.3   | 2.2   | 1.9   | 1.3   | 2.3   | 2.7   | 2.8   | 2.2   | 2.5   | 2.7   |
|           | St. d.  | 10.2               | 9.1  | 10.3  | 9.9   | 8.1   | 5.9   | 9.9   | 9.8   | 12.9  | 9.3   | 6.0   | 8.9   |
|           | C. of v | 18.4               | 16.2 | 19.0  | 19.5  | 16.9  | 11.1  | 19.5  | 17.4  | 23.4  | 16.4  | 11.7  | 13.3  |
| 150-175   | No.     | 108                | 42   | 70    | 63    | 54    | 94    | 44    | 93    | 46    | 51    | 18    | 30    |
|           | Mean    | 72.4               | 70.7 | 67.7  | 68.0  | 66.9  | 67.9  | 70.9  | 69.5  | 70.1  | 74.1  | 73.0  | 74.3  |
|           | S. e.   | 1.2                | 1.8  | 1.4   | 1.2   | 1.1   | 0.9   | 1.9   | 1.1   | 1.7   | 1.6   | 3.1   | 2.0   |
|           | St. d.  | 12.6               | 11.6 | 11.8  | 9.4   | 7.8   | 8.3   | 12.3  | 10.8  | 11.0  | 11.0  | 12.6  | 10.3  |
|           | C. of v | 17.4               | 16.4 | 17.4  | 13.8  | 11.7  | 12.5  | 17.3  | 15.5  | 15.7  | 14.8  | 16.8  | 14.1  |
| 180-205   | No.     | 22                 | 1    | 40    | 30    | 32    | 44    | 21    | 45    | 33    | 56    | 22    | 51    |
|           | Mean    | 91.8               | 80   | 88.8  | 89.5  | 85.3  | 86.3  | 81.7  | 89.6  | 89.4  | 92.4  | 93.9  | 97.2  |
|           | S. e.   | 2.7                |      | 2.1   | 2.6   | 3.6   | 1.6   | 3.1   | 1.8   | 2.3   | 1.7   | 2.4   | 1.4   |
|           | St. d.  | 12.4               |      | 12.9  | 13.9  | 19.8  | 10.5  | 13.8  | 12.2  | 12.7  | 12.8  | 10.9  | 10.1  |
|           | C. of v | 13.5               |      | 14.5  | 15.6  | 23.2  | 12.2  | 16.9  | 13.6  | 14.2  | 13.9  | 11.6  | 10.4  |
| ≥ 210     | No.     |                    |      | 3     | 5     | 20    | 47    | 24    | 44    | 8     | 32    | 10    | 36    |
|           | Mean    |                    |      | 93.3  | 110.0 | 117.8 | 105.0 | 102.5 | 107.7 | 108.8 | 119.8 | 120.0 | 118.6 |
|           | S. e.   |                    |      | 9.0   | 6.9   | 7.4   | 2.3   | 3.6   | 1.9   | 7.3   | 2.9   | 4.7   | 2.7   |
|           | St. d.  |                    |      | 12.7  | 13.7  | 32.2  | 15.2  | 17.4  | 12.2  | 19.2  | 16.1  | 14.1  | 16.2  |
|           | C. of v |                    |      | 13.6  | 12.5  | 27.3  | 14.5  | 17.0  | 11.3  | 17.6  | 13.4  | 11.8  | 13.7  |

Table 6.10 The pulse pressure in 1951-52 by age and sex  
Mean, standard of the mean, standard deviation, and coefficient of variation

| BP groups | 1950    | Age and sex groups |      |       |       |       |      |       |      |       |       |      |       |
|-----------|---------|--------------------|------|-------|-------|-------|------|-------|------|-------|-------|------|-------|
|           |         | 15-29              |      | 30-39 |       | 40-49 |      | 50-59 |      | 60-69 |       | ≥ 70 |       |
|           |         | M                  | F    | M     | F     | M     | F    | M     | F    | M     | F     | M    | F     |
| ≤ 145     | No.     | 14                 | 19   | 21    | 22    | 20    | 19   | 19    | 14   | 22    | 20    | 7    | 12    |
|           | Mean    | 48.2               | 51.4 | 48.6  | 50.7  | 49.8  | 51.3 | 51.8  | 57.1 | 57.5  | 56.5  | 65.0 | 72.1  |
|           | S. e.   | 2.0                | 2.0  | 2.1   | 1.3   | 1.6   | 2.6  | 2.1   | 2.2  | 3.4   | 2.2   | 11.5 | 5.0   |
|           | St. d.  | 8.3                | 7.3  | 9.4   | 5.9   | 7.1   | 11.0 | 8.8   | 8.0  | 15.7  | 9.4   | 28.2 | 16.4  |
|           | C. of v | 17.2               | 14.2 | 19.3  | 11.6  | 14.3  | 21.4 | 17.0  | 14.0 | 27.3  | 16.7  | 43.4 | 22.7  |
| 150-175   | No.     | 108                | 42   | 70    | 65    | 54    | 94   | 44    | 93   | 46    | 51    | 18   | 30    |
|           | Mean    | 57.4               | 57.3 | 53.1  | 55.1  | 56.6  | 64.0 | 62.0  | 65.5 | 69.8  | 73.9  | 65.6 | 80.3  |
|           | S. e.   | 1.1                | 1.9  | 1.2   | 1.3   | 1.4   | 1.1  | 2.7   | 1.2  | 3.0   | 2.3   | 5.4  | 2.3   |
|           | St. d.  | 11.4               | 11.9 | 10.2  | 10.3  | 10.4  | 10.5 | 17.4  | 11.7 | 19.9  | 15.9  | 22.2 | 13.3  |
|           | C. of v | 19.9               | 20.8 | 19.2  | 18.7  | 18.4  | 16.4 | 28.1  | 17.9 | 28.5  | 21.5  | 33.8 | 16.6  |
| 180-205   | No.     | 22                 | 1    | 40    | 30    | 32    | 44   | 21    | 45   | 33    | 56    | 22   | 51    |
|           | Mean    | 76.4               | 100  | 74.4  | 72.3  | 73.3  | 74.9 | 76.4  | 87.0 | 80.6  | 86.1  | 84.3 | 91.8  |
|           | S. e.   | 3.9                |      | 2.2   | 2.2   | 2.6   | 2.4  | 3.3   | 2.5  | 4.4   | 2.0   | 3.1  | 2.1   |
|           | St. d.  | 17.9               |      | 13.9  | 11.5  | 14.4  | 13.6 | 14.6  | 16.2 | 25.0  | 15.0  | 14.4 | 14.7  |
|           | C. of v | 23.4               |      | 18.7  | 15.9  | 19.6  | 20.8 | 19.1  | 18.6 | 31.0  | 17.4  | 17.1 | 16.0  |
| ≥ 210     | No.     |                    |      | 3     | 5     | 20    | 47   | 24    | 44   | 8     | 32    | 10   | 36    |
|           | Mean    |                    |      | 71.7  | 109.0 | 91.8  | 95.1 | 88.8  | 95.5 | 102.5 | 103.1 | 88.5 | 102.8 |
|           | S. e.   |                    |      | 4.1   | 9.5   | 4.3   | 2.5  | 4.6   | 3.3  | 4.5   | 2.6   | 12.2 | 4.3   |
|           | St. d.  |                    |      | 5.2   | 19.0  | 18.8  | 16.8 | 22.2  | 21.4 | 11.9  | 14.4  | 36.6 | 25.6  |
|           | C. of v |                    |      | 7.2   | 17.4  | 20.5  | 17.7 | 25.0  | 22.4 | 11.6  | 14.0  | 41.4 | 24.9  |

difference with increasing age in the same blood pressure group. On the other hand the range does increase with rising blood pressure within the same age group.

The histograms for the 1951-52 measurements show nearly the same distribution as the 1950 histograms. There is a tendency in both sexes to greater dispersion in the higher age groups compared to the 1950 measurements.

The mean values of the 1951-52 measurements are on the whole lower. This is seen most clearly in the groups with high blood pressures, while the group of ≤ 145 mm shows the same or a slight increase of the pulse pressure.

a) *Analysis of the mean values of the groups*  
The drop in the 1951-52 values is due to the combination of lower systolic and

higher diastolic blood pressure values. This is seen in all groups except those with a blood pressure ≤ 145 in both sexes. This decrease is most distinct in the younger age groups with high blood pressures. The difference between the two measurements is illustrated in Fig. 6.17.

The pulse pressure in 1951-52 increases with age in all blood pressure groups in both sexes. The increase is most marked in the lower blood pressure groups. The same was observed of the systolic blood pressure.

b) *The difference between the pulse pressure in 1950 and in 1951-52*

The difference in the pulse pressure has been calculated in the same way as described for the systolic and diastolic blood pressures.

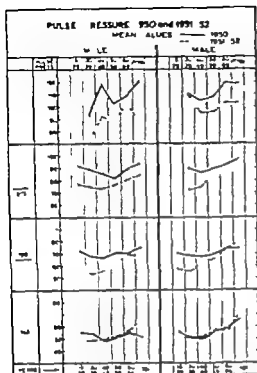
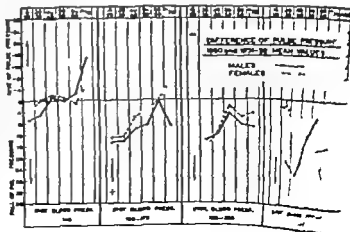


Fig. 6.17 The mean values of the pulse pressure in 1950 and in 1951-52 are shown for each of the four blood pressure groups, divided according to age and sex. The series is grouped according to the systolic blood pressure in 1950. The Figure shows the lower pulse pressure of the study groups in 1951-52 compared to 1950. The difference is greatest in the younger age groups.

Fig. 6.18. The Figure shows the mean rise or fall in the pulse pressure for the groups studied according to the height of their original pressure. Points of reference are given in detail in Figure 6.8. The pulse pressure curves follow the trend presented by the systolic blood pressure to some extent.



These calculations have not been set up in histograms as they would not show anything particularly new. The dispersion of the readings, expressed by the standard deviation or standard error of the mean shows a marked increase in the groups with higher blood pressures in the same age groups, but no increase with age within the same blood pressure groups (Table II 11).

The mean values of these differences also decreased from 1950 to 1951-52.

Figure 6.18 shows the great similarity to the differences of the systolic blood pressure in both sexes (see Fig. 6.8). One finds the same linear progress of the mean values with increasing age in every blood pressure group. However the mean differences are not so great as for the systolic blood pressure and the lines do not follow the steep course taken by the systolic differences.

There is good agreement between the two sexes in all the blood pressure groups, as there was for the systolic blood pressure.

## Summary and conclusions

Analysis of the pulse pressure follows the lines described for systolic and diastolic blood pressures.

The mean values of the 1951-52 measurements are on the whole lower than in 1950. This drop is due to the combination

Table 6.11 The difference between the pulse pressure in 1950 and in 1951-52 by age and sex  
Mean, standard error of the mean, and standard deviation

| BP groups | 1950   | Age and sex groups |      |       |      |       |      |       |      |       |      |       |      |
|-----------|--------|--------------------|------|-------|------|-------|------|-------|------|-------|------|-------|------|
|           |        | 15-29              |      | 30-39 |      | 40-49 |      | 50-59 |      | 60-69 |      | ≥ 70  |      |
|           |        | M                  | F    | M     | F    | M     | F    | M     | F    | M     | F    | M     | F    |
| ≤ 145     | No.    | 19                 | 14   | 21    | 22   | 20    | 19   | 19    | 14   | 22    | 20   | 7     | 12   |
|           | Mean   | 7.1                | 4.6  | 3.7   | 0    | -1.8  | -1.6 | 0.3   | -0.7 | -2.3  | 1    | -13.6 | -5.4 |
|           | S. e.  | 2.3                | 2.7  | 2.3   | 2.6  | 2.1   | 2.4  | 2.0   | 4.3  | 2.8   | 3.0  | 10.7  | 4.8  |
|           | St. d. | 10.5               | 9.5  | 11.4  | 11.8 | 9.1   | 10.3 | 8.3   | 15.4 | 12.9  | 13.4 | 26.2  | 13.8 |
| 150-175   | No.    | 108                | 42   | 70    | 65   | 54    | 94   | 44    | 93   | 46    | 51   | 18    | 30   |
|           | Mean   | 15.0               | 13.3 | 14.6  | 12.9 | 10.3  | 5.9  | 8.9   | 3.9  | 0.5   | 0.1  | 9.4   | -5.8 |
|           | S. e.  | 1.5                | 2.0  | 1.6   | 1.6  | 1.5   | 1.1  | 2.4   | 1.4  | 3.3   | 2.5  | 5.0   | 3.0  |
|           | St. d. | 15.2               | 13.0 | 13.1  | 12.4 | 11.1  | 11.2 | 13.8  | 13.8 | 22.0  | 17.8 | 20.7  | 16.2 |
| 180-205   | No.    | 22                 | 1    | 40    | 30   | 32    | 44   | 21    | 45   | 33    | 56   | 22    | 53   |
|           | Mean   | 15.5               | -20  | 14.4  | 17.0 | 12.0  | 11.4 | 5.2   | 2.6  | 8.8   | 6.3  | 9.6   | 5.2  |
|           | S. e.  | 4.2                |      | 2.3   | 3.3  | 3.8   | 2.6  | 4.2   | 2.5  | 4.6   | 2.4  | 3.1   | 2.3  |
|           | St. d. | 19.3               |      | 14.6  | 18.6 | 21.1  | 1.0  | 18.6  | 16.5 | 26.1  | 17.7 | 14.5  | 17.8 |
| ≥ 210     | No.    |                    |      | 3     | 5    | 20    | 47   | 24    | 44   | 8     | 32   | 10    | 36   |
|           | Mean   |                    |      | 21.7  | 1.0  | 26.0  | 9.9  | 13.8  | 12.3 | 6.3   | 16.7 | 31.5  | 15.8 |
|           | S. e.  |                    |      | 9.2   | 9.7  | 3.0   | 2.8  | 3.0   | 3.4  | 6.9   | 2.8  | 10.5  | 4.9  |
|           | St. d. |                    |      | 13.0  | 19.3 | 21.7  | 18.7 | 24.2  | 22.5 | 18.3  | 15.7 | 31.5  | 29.0 |

of lower systolic and higher diastolic blood pressure values and is most distinct in the younger age groups with high blood pressures.

The pulse pressure on the whole shows the same changes with age and blood

pressure that have been described for the systolic blood pressure.

The calculations verify that the variations in the pulse pressure mainly follow the alterations in the systolic blood pressure.

## II The blood pressure distribution 1951-52

### Sitting, lying and after 30 minutes rest

#### Introduction

The distribution of the blood pressure values measured in the sitting position, in 1950 and 1951-52 has been presented in the earlier pages. The calculations have been done on a grouped series based on a stratification of the systolic blood pressure in 1950. This grouping has been used consistently in all calculations and the groups in 1950 and 1951-52 contain the same individuals.

When investigating the series in 1951-52 the blood pressure was measured several times sitting lying and after 30 minutes rest. These measurements were all taken by the

same investigator myself using the same methods.

These measurements form the basis of the following study.

The measurements in 1951-52, in contrast to the casual blood pressures in 1950, involved three readings in each of the three positions. Another reason for using these measurements is the varying time interval between the measurements in 1950 and the investigation in 1951-52. This time interval has varied from 9 months to a maximum of 2 years. It must be realized that in this time interval pro-

gression of any underlying hypertensive disease could have occurred in some of the individuals. It can therefore hardly be correct to relate the observations in 1951-52 to the measurements taken in 1950.

However one must realize that with such a method one must abandon the original grouping of the series. Some individuals have shown a rise, others a fall in blood pressure. A grouping of the series based upon the 1951-52 observations with the same class intervals as used in 1950 will therefore include several individuals previously classified in a lower or higher blood pressure group. On closer study of the previous and the following histograms one can find out how many of the individuals belong to a higher or lower blood pressure group within the same age group. Even though the mode shows relatively little variation in the majority of the groups, a considerable shift is to be seen.

In the following section this material is analysed in two ways according to the 1951-52 measurements

- 1) by stratification of the *systolic* blood pressure,
- 2) by stratification of the *diastolic* blood pressure.

The series is divided into blood pressure groups in which the *systolic* blood pressure has the same class-limits and class-intervals as the 1950 series. This can at first sight give the impression that it is the same groups of individuals who are under review. This is not the case. Purely practical reasons have been taken into consideration here. The class-limits  $\geq 145$ , 150-175, 180-205, and  $\geq 210$  were coded on punch-cards and transferred to all data cards. It was therefore convenient to use the same grouping as in 1950. It must also be emphasized that the age groups remain unaltered. Each of the six age groups still contains the same individuals as in 1950. Thus the shift of the individuals takes place only from the lower or higher blood pressure group of the same age.

In addition one wants to analyse the

series grouped according to the *diastolic* blood pressure, ranging from low to high values. The class-limits and class-intervals are  $\leq 85$ , 90-100, 105-115 and  $\geq 120$  mm Hg.

The blood pressure measured in the *sitting position* is used in both classifications. In addition it is necessary to investigate the same groups according to the blood pressure after 30 minutes rest.

In many cases it is necessary to combine some of the cells to acquire enough material.

### The systolic blood pressure in the sitting position

The total number of individuals in each cell (group) is different from that in the 1950 grouping. This is due to the shift of the individuals from higher or lower blood pressure groups within the same age group as mentioned above. One finds more individuals with lower blood pressure in the younger age groups, while the shift is less pronounced among the older individuals. In several groups with high blood pressure the total number of individuals increased.

#### a) The mean values of the systolic blood pressure

##### 1) Stratification according to the systolic blood pressure

From this classification one sees that the mean values (Table 6.12) are about the same in each age group in each of the 4 blood pressure groups. However there is a slight tendency to an increase in the mean blood pressure in both sexes in the three lower blood pressure groups, while the highest shows a decrease with increasing age in women. This tendency to increase with age was also seen when the series was classified according to the systolic blood pressure in 1950 (see p. 74).

There is little difference in the mean values of the groups compared to the 1950 values. This is due to the fact that the same class-limits have been used for this classification.

The dispersion expressed by the standard deviation and the standard error of the



Table 6.12. Systolic blood pressure in 1951-52 by age and sex  
Series grouped according to the systolic blood pressure  
Mean, standard of the mean, and standard deviation

| BP groups<br>1951-52 |        | Age and sex groups |       |       |       |       |       |       |       |       |       |       |       |
|----------------------|--------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                      |        | 15-29              |       | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|                      |        | M                  | F     | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| ≤ 145                | No.    | 67                 | 32    | 56    | 44    | 39    | 33    | 28    | 27    | 20    | 15    | 8     | 10    |
|                      | Mean   | 133.9              | 135.9 | 132.9 | 131.1 | 136.3 | 133.9 | 133.4 | 139.8 | 135.3 | 137.3 | 133.8 | 141.0 |
|                      | S. e.  | 1.2                | 1.6   | 1.3   | 1.5   | 1.3   | 1.2   | 1.9   | 0.9   | 1.7   | 1.9   | 3.2   | 1.8   |
| 150-179              | No.    | 74                 | 4     | 64    | 39    | 51    | 96    | 40    | 79    | 40    | 45    | 20    | 23    |
|                      | Mean   | 156.9              | 159.6 | 159.4 | 159.0 | 161.8 | 161.7 | 159.6 | 161.2 | 161.6 | 161.1 | 164   | 163.3 |
|                      | S. e.  | 0.9                | 1     | 1.0   | 1.1   | 1.2   | 0.9   | 1.3   | 1.0   | 1.4   | 1.3   | 2.1   | 1.7   |
| 180-209              | No.    | 8                  |       | 11    | 14    | 23    | 41    | 26    | 50    | 31    | 38    | 21    | 57    |
|                      | Mean   | 186.3              |       | 185.9 | 188.7 | 188.5 | 188.5 | 190.6 | 189.3 | 184.4 | 190.8 | 190.2 | 191.9 |
|                      | S. e.  | 2.8                |       | 2.2   | 2.3   | 1.7   | 1.5   | 1.7   | 1.2   | 1.5   | 1.1   | 2.0   | 1.1   |
| ≥ 210                | No.    |                    | 1     | 3     | 5     | 13    | 34    | 14    | 40    | 18    | 41    | 6     | 39    |
|                      | Mean   |                    | 240   | 211   | 243.0 | 217.3 | 227.5 | 224.6 | 229.6 | 221.9 | 225.5 | 221.3 | 226.5 |
|                      | S. e.  |                    |       | 1.6   | 11.2  | 3.2   | 2.9   | 3.9   | 2.9   | 3.5   | 2.7   | 3.9   | 2.4   |
|                      | St. d. |                    |       | 2.2   | 22.3  | 11.2  | 16.7  | 14.0  | 18.1  | 14.3  | 16.7  | 10.5  | 8.1   |

Table 6.13. Systolic blood pressure in 1951-52 by age and sex  
Series grouped according to the diastolic blood pressure  
Mean, standard error of the mean, and standard deviation

| BP groups<br>1951-52 |        | Age and sex groups |       |       |       |       |       |       |       |       |       |       |       |
|----------------------|--------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                      |        | 15-29              |       | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|                      |        | M                  | F     | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| ≤ 85                 | No.    | 50                 | 14    | 35    | 34    | 19    | 21    | 70    | 19    | 17    | 1     | 10    | 14    |
|                      | Mean   | 138.8              | 131.8 | 139.6 | 131.5 | 138.2 | 142.9 | 144.5 | 143.5 | 148.5 | 137.1 | 157.0 | 147.3 |
|                      | S. e.  | 2.1                | 2.9   | 2.7   | 2.3   | 3.9   | 3.3   | 3.8   | 2.9   | 6.4   | 2.6   | 8.0   | 2.8   |
| 90-100               | No.    | 92                 | 41    | 85    | 60    | 65    | 105   | 48    | 96    | 55    | 76    | 23    | 62    |
|                      | Mean   | 152.2              | 150.7 | 154.5 | 154.6 | 154.6 | 159.4 | 154.4 | 163.0 | 166.8 | 172.6 | 170.9 | 185.2 |
|                      | S. e.  | 1.5                | 2.1   | 1.7   | 1.7   | 1.9   | 1.6   | 2.3   | 1.8   | 3.0   | 2.3   | 5.6   | 2.5   |
| 105-115              | No.    | 7                  | 1     | 10    | 20    | 23    | 48    | 23    | 44    | 26    | 42    | 21    | 31    |
|                      | Mean   | 161.4              | 155   | 170.0 | 173.8 | 182.8 | 183.6 | 187.1 | 193.4 | 184.6 | 195.6 | 188.6 | 206.1 |
|                      | S. e.  | 4.0                |       | 4.2   | 3.5   | 3.9   | 2.4   | 4.7   | 3.3   | 5.4   | 2.1   | 4.1   | 5.2   |
| ≥ 120                | No.    |                    | 1     | 4     | 8     | 19    | 30    | 17    | 37    | 11    | 29    | 3     | 21    |
|                      | Mean   |                    | 240   | 202.3 | 222.5 | 202.4 | 223.3 | 21.6  | 222.6 | 223.0 | 229.0 | 218.3 | 227.5 |
|                      | S. e.  |                    |       | 6.0   | 12.9  | 4.7   | 3.8   | 4.8   | 4.8   | 4.5   | 3.6   | 12.8  | 3.5   |
|                      | St. d. |                    |       | 10.3  | 32.0  | 19.9  | 20.3  | 19.0  | 23.0  | 13.8  | 19.0  | 18.4  | 16.3  |

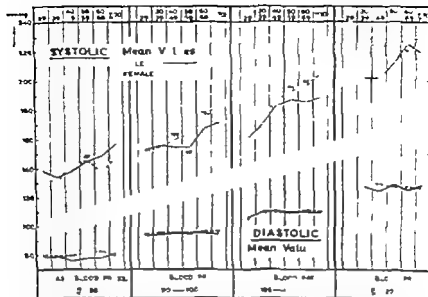


Fig. 6.19 Systolic and diastolic blood pressure in sitting position. The material is grouped according to the diastolic blood pressure 1951-52. The mean values of the systolic blood pressure rise with increasing age in all 4 blood pressure groups except for the women in the group  $\geq 120$  mm Hg. The mean values of the diastolic blood pressure are almost the same in the age groups within each of the four blood pressure strata.

mean is about the same as in the 1930 grouping. In general the dispersion is greatest in the higher blood pressure groups and more pronounced in women.

## 2) Stratification according to the diastolic blood pressure

From Table 6.13 it can be seen that the total number of individuals in each of the groups is different from that in the systolic classification. Further the mean values of the systolic blood pressure rise steeply with age in all 4 blood pressure groups, except for the women in the group  $\geq 120$  mm Hg. This increase is more pronounced in women in the two central blood pressure groups. The increase with age follows an almost linear course in the three lower blood pressure groups. This is shown in Fig. 6.19.

The dispersion expressed by the standard deviation and the standard error of the mean is markedly greater than with the systolic classification. This is a natural

result of the grouping and illustrates how groups with the same diastolic blood pressure have very different systolic blood pressures.

The pulse pressure is about the same in the younger age groups in the three lower blood pressure groups. In the middle and higher age groups there is a consistent rise with increasing blood pressure.

## b) The difference between the systolic blood pressure in the sitting and lying positions and after 30 minutes' rest

In this section the differences in the systolic blood pressure in these positions will be presented. The calculations have been done on the group means and the material is grouped in two ways: by stratification of 1) the systolic and 2) the diastolic blood pressures, keeping the class-limits mentioned above (p. 93).

The mean values of the differences in all 24 cells in both sexes are shown in Tables

Table 6.14 The difference between the systolic blood pressure in the sitting and lying position by age and sex  
Series grouped according to the systolic blood pressure

| IDP-groups 1951-52<br>systolic | Age and sex groups             |                            |                            |                             |                            |  |                             |                            |  |                            |                            |                            |
|--------------------------------|--------------------------------|----------------------------|----------------------------|-----------------------------|----------------------------|--|-----------------------------|----------------------------|--|----------------------------|----------------------------|----------------------------|
|                                | 15-29                          |                            |                            | 30-39                       |                            |  | 40-49                       |                            |  | 50-59                      |                            |                            |
|                                | M                              | F                          |                            | M                           | F                          |  | M                           | F                          |  | M                          | F                          |                            |
| 145                            | No.<br>Mean $\pm$ s.e.<br>S.D. | 67<br>6.2 $\pm$ 0.7<br>5.9 | 32<br>4.8 $\pm$ 0.9<br>4.9 | 55<br>5.3 $\pm$ 0.6<br>4.4  | 44<br>4.4 $\pm$ 0.7<br>4.5 |  | 39<br>3.8 $\pm$ 0.6<br>3.6  | 33<br>3.2 $\pm$ 0.8<br>4.3 |  | 28<br>2.3 $\pm$ 1.0<br>5.2 | 27<br>3.9 $\pm$ 0.9<br>4.5 | 19<br>2.6 $\pm$ 1.0<br>4.1 |
| 175                            | No.<br>Mean $\pm$ s.e.<br>S.D. | 71<br>8.5 $\pm$ 0.9<br>7.3 | 24<br>7.1 $\pm$ 1.7<br>8.0 | 64<br>9.1 $\pm$ 0.5<br>4.3  | 59<br>8.2 $\pm$ 0.7<br>5.2 |  | 51<br>7.6 $\pm$ 0.9<br>6.3  | 96<br>6.5 $\pm$ 0.6<br>6.2 |  | 39<br>3.8 $\pm$ 1.3<br>7.7 | 79<br>4.9 $\pm$ 0.7<br>6.2 | 41<br>4.4 $\pm$ 1.2<br>7.3 |
| 205                            | No.<br>Mean $\pm$ s.e.<br>S.D. | 7<br>12.9 $\pm$ 2.8<br>6.9 |                            | 11<br>10.9 $\pm$ 2.4<br>7.6 | 14<br>4.5 $\pm$ 1.4<br>4.9 |  | 23<br>4.8 $\pm$ 1.6<br>7.5  | 41<br>6.5 $\pm$ 1.2<br>7.4 |  | 24<br>9.4 $\pm$ 1.8<br>8.4 | 49<br>5.1 $\pm$ 0.8<br>5.5 | 31<br>6.5 $\pm$ 1.3<br>7.1 |
| 210                            | No.<br>Mean $\pm$ s.e.<br>S.D. |                            | 1<br>15.0                  | 2<br>17.5 $\pm$ 7.5<br>7.5  | 5<br>7.0 $\pm$ 3.7<br>7.4  |  | 13<br>11.5 $\pm$ 2.0<br>6.9 | 31<br>5.5 $\pm$ 1.5<br>8.1 |  | 15<br>9.2 $\pm$ 2.5<br>7.8 | 25<br>7.8 $\pm$ 1.4<br>8.8 | 17<br>7.1 $\pm$ 1.7<br>6.3 |

The difference between the systolic blood pressure in lying position and after reading 90 minutes

| IDP-groups 1951-52<br>systolic | Age and sex groups             |                             |                             |                             |                             |  |                              |                              |  |                              |                              |                              |
|--------------------------------|--------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|--|------------------------------|------------------------------|--|------------------------------|------------------------------|------------------------------|
|                                | 15-29                          |                             |                             | 30-39                       |                             |  | 40-49                        |                              |  | 50-59                        |                              |                              |
|                                | M                              | F                           |                             | M                           | F                           |  | M                            | F                            |  | M                            | F                            |                              |
| 145                            | No.<br>Mean $\pm$ s.e.<br>S.D. | 67<br>6.4 $\pm$ 0.9<br>7    | 32<br>6.6 $\pm$ 1.1<br>6.1  | 35<br>4.9 $\pm$ 0.8<br>6.2  | 44<br>5.6 $\pm$ 0.9<br>6.0  |  | 39<br>8.5 $\pm$ 1.3<br>7.9   | 33<br>5.2 $\pm$ 1.2<br>6.7   |  | 28<br>7.0 $\pm$ 1.5<br>6.6   | 27<br>5.9 $\pm$ 1.3<br>6.8   | 19<br>5.5 $\pm$ 1.7<br>7.2   |
| -175                           | No.<br>Mean $\pm$ s.e.<br>S.D. | 74<br>10.6 $\pm$ 0.9<br>7.4 | 24<br>15.8 $\pm$ 1.8<br>8.4 | 64<br>11.6 $\pm$ 1.0<br>8.0 | 59<br>9.9 $\pm$ 0.9<br>6.8  |  | 51<br>11.1 $\pm$ 1.5<br>9.1  | 96<br>11.2 $\pm$ 0.9<br>8.7  |  | 39<br>8.2 $\pm$ 1.7<br>10.4  | 79<br>7.6 $\pm$ 1.1<br>9.7   | 41<br>7.0 $\pm$ 1.4<br>8.7   |
| -205                           | No.<br>Mean $\pm$ s.e.<br>S.D. | 7<br>15.7 $\pm$ 2.0         |                             | 11<br>15.9 $\pm$ 4.5<br>7.5 | 14<br>22.1 $\pm$ 3.6<br>6.7 |  | 23<br>16.5 $\pm$ 2.6<br>10.7 | 41<br>14.1 $\pm$ 1.6<br>11.7 |  | 24<br>11.7 $\pm$ 2.4<br>12.5 | 49<br>12.8 $\pm$ 1.5<br>10.0 | 31<br>10.8 $\pm$ 1.8<br>10.0 |
| 210                            | No.<br>Mean $\pm$ s.e.<br>S.D. |                             | 1<br>10.0                   | 2<br>7.5 $\pm$ 7.5<br>7.5   | 5<br>8.0 $\pm$ 3.4<br>6.7   |  | 13<br>18.5 $\pm$ 3.1<br>10.7 | 31<br>18.7 $\pm$ 2.2<br>11.7 |  | 13<br>16.2 $\pm$ 3.6<br>12.5 | 39<br>12.8 $\pm$ 1.9<br>11.9 | 17<br>14.7 $\pm$ 3.5<br>14.1 |

Table 6.15. The difference between the systolic blood pressure in the sitting and lying position by age and sex  
 \*Subjects grouped according to the diastolic blood pressure

| BP-groups 1931-52<br>diastolic | Age and sex groups            |                        |                        |                         |                        |                         |                        |                        |                        |                        |                        |                         |
|--------------------------------|-------------------------------|------------------------|------------------------|-------------------------|------------------------|-------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|-------------------------|
|                                | 15-20                         |                        | 30-39                  |                         | 40-49                  |                         | 50-59                  |                        | 60-69                  |                        | ≥ 70                   |                         |
|                                | M                             | F                      | M                      | F                       | M                      | F                       | M                      | F                      | M                      | F                      | M                      | F                       |
| ≤ 85                           | No.<br>Mean ± s.e.<br>S.E. d. | 14<br>4.3 ± 1.4<br>4.9 | 54<br>4.0 ± 0.8<br>4.5 | 34<br>4.9 ± 0.8<br>4.8  | 19<br>3.0 ± 0.9<br>3.6 | 21<br>3.1 ± 0.9<br>3.9  | 19<br>3.9 ± 1.4<br>6.0 | 19<br>3.9 ± 1.2<br>5.0 | 13<br>3.3 ± 1.5<br>3.6 | 12<br>1.7 ± 2.2<br>7.1 | 9<br>-2.8 ± 1.5<br>4.1 | 14<br>-1.4 ± 2.3<br>8.3 |
| 90-100                         | No.<br>Mean ± s.e.<br>S.E. d. | 92<br>8.5 ± 0.8<br>7.5 | 85<br>8.5 ± 0.6<br>5.4 | 100<br>7.0 ± 0.7<br>5.4 | 65<br>7.8 ± 0.6<br>5.1 | 101<br>8.5 ± 0.6<br>6.1 | 47<br>4.0 ± 1.1<br>7.4 | 86<br>3.2 ± 0.5<br>5.1 | 56<br>5.3 ± 1.0<br>7.6 | 74<br>3.1 ± 0.8<br>6.7 | 72<br>3.9 ± 1.7<br>7.6 | 65<br>2.6 ± 1.4<br>10.9 |
| 105-115                        | No.<br>Mean ± s.e.<br>S.E. d. | 6<br>9.2 ± 0.8<br>1.6  | 10<br>6.5 ± 1.3<br>5.9 | 70<br>6.0 ± 1.0<br>4.3  | 25<br>6.1 ± 1.7<br>8.1 | 48<br>5.6 ± 1.0<br>7.1  | 21<br>8.6 ± 1.5<br>6.8 | 42<br>6.1 ± 1.1<br>7.0 | 26<br>4.6 ± 1.0<br>5.1 | 42<br>5.3 ± 1.3<br>8.5 | 20<br>3.3 ± 1.5<br>6.5 | 30<br>1.5 ± 1.3<br>6.9  |
| ≥ 120                          | No.<br>Mean ± s.e.<br>S.E. d. | 1<br>15.0              | 3<br>16.7 ± 4.3<br>6.1 | 8<br>8.8 ± 2.8<br>7.3   | 19<br>6.8 ± 2.0<br>8.3 | 20<br>6.5 ± 1.7<br>8.7  | 15<br>9.0 ± 2.5<br>9.5 | 37<br>6.9 ± 1.5<br>9.2 | 11<br>7.7 ± 2.4<br>7.5 | 29<br>6.2 ± 1.7<br>9.0 | 3<br>-8.3 ± 4.4<br>6.2 | 21<br>1.9 ± 1.6<br>7.1  |

The difference between the systolic blood pressure in the lying position and after raising 30 minutes

| BP-groups 1931-52<br>diastolic | Age and sex groups            |                         |                         |                          |                          |                          |                          |                          |                          |                          |                          |                          |
|--------------------------------|-------------------------------|-------------------------|-------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                                | 15-20                         |                         | 30-39                   |                          | 40-49                    |                          | 50-59                    |                          | 60-69                    |                          | ≥ 70                     |                          |
|                                | M                             | F                       | M                       | F                        | M                        | F                        | M                        | F                        | M                        | F                        | M                        | F                        |
| ≤ 85                           | No.<br>Mean ± s.e.<br>S.E. d. | 50<br>8.6 ± 1.0<br>6.6  | 14<br>5.0 ± 1.8<br>5.6  | 91<br>4.4 ± 1.2<br>6.6   | 19<br>4.9 ± 1.1<br>8.3   | 2<br>7.4 ± 2.4<br>10.6   | 19<br>6.3 ± 2.3<br>9.8   | 19<br>8.1 ± 2.1<br>10.1  | 13<br>5.5 ± 2.0<br>7.6   | 12<br>6.7 ± 2.7<br>8.9   | 9<br>11.7 ± 1.1<br>3.9   | 14<br>11.8 ± 2.7<br>9.7  |
| 90-100                         | No.<br>Mean ± s.e.<br>S.E. d. | 92<br>10.1 ± 0.8<br>7.7 | 85<br>12.1 ± 1.3<br>6.5 | 100<br>11.2 ± 1.0<br>7.7 | 65<br>10.9 ± 1.1<br>8.7  | 104<br>10.7 ± 0.8<br>8.5 | 47<br>9.7 ± 1.3<br>8.8   | 86<br>8.8 ± 1.0<br>9.9   | 56<br>8.6 ± 1.3<br>9.9   | 74<br>6.1 ± 1.0<br>8.1   | 72<br>6.6 ± 1.9<br>8.8   | 65<br>8.7 ± 1.1<br>8.5   |
| 105-115                        | No.<br>Mean ± s.e.<br>S.E. d. | 6<br>10.8 ± 1.0<br>6.8  | 1<br>23.0               | 10<br>18.0 ± 2.1<br>6.3  | 20<br>12.5 ± 2.4<br>10.4 | 48<br>13.2 ± 1.5<br>10.1 | 23<br>12.0 ± 2.8<br>15.2 | 42<br>8.9 ± 1.8<br>10.5  | 26<br>10.2 ± 1.8<br>9.1  | 42<br>8.9 ± 1.7<br>10.6  | 20<br>12.5 ± 2.4<br>10.4 | 30<br>7.5 ± 2.2<br>11.6  |
| ≥ 120                          | No.<br>Mean ± s.e.<br>S.E. d. | 1<br>10.1               | 3<br>13.5 ± 1.8<br>2.5  | 8<br>12.5 ± 5.3<br>13.9  | 19<br>14.7 ± 2.1<br>9.0  | 28<br>17.9 ± 2.2<br>11.4 | 15<br>10.5 ± 2.8<br>10.4 | 37<br>13.8 ± 1.7<br>10.4 | 11<br>13.6 ± 4.9<br>13.5 | 29<br>12.2 ± 2.1<br>10.9 | 3<br>13.3 ± 6.7<br>9.1   | 21<br>15.7 ± 2.5<br>11.2 |

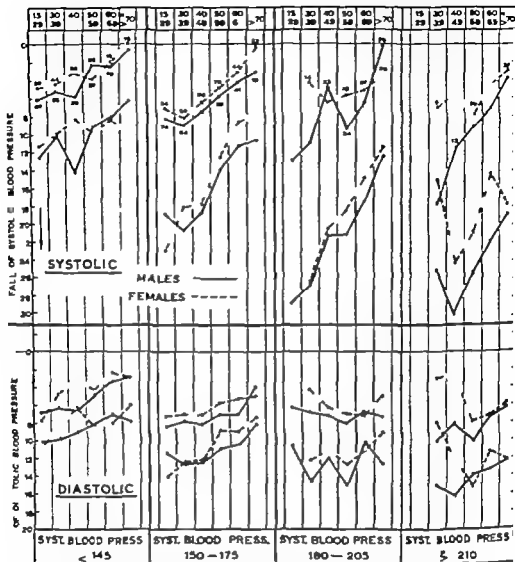


Fig 6.20 The difference in the mean systolic and diastolic blood pressure in the sitting lying positions for both sexes is shown by the upper lines, and the difference between the sitting and resting mean blood pressure is shown by the lower lines. The total number of individuals in each group can be seen from the numbers given for the systolic blood pressure in the upper part of the diagram. The blood pressure in the sitting position is used as the base line (0). The material is grouped according to the systolic blood pressure.

6.14 and 6.15 The dispersion is given by the standard deviation and the standard error of the mean.

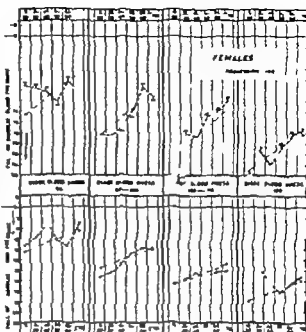
In order to facilitate the study of all these Tables and to simplify the presentation the blood pressure differences in

the different positions have been illustrated diagrammatically.

The difference between the systolic blood pressure in the two sexes is presented in the upper part of Fig 6.20 and in 6.21.

### 1) Stratification according to the systolic blood pressure

There is a consistent regularity in these differences in both sexes. The fall in the blood pressure is greatest in the groups with high blood pressure, and in each of the blood pressure groups it is evident that the fall is greatest in the younger individuals. Further the difference in the blood pressure is greatest in men in nearly all the groups. The difference between the two sexes is inconsiderable in the lower blood pressure groups but is marked in the  $\geq 210$  mm Hg group. These calculations show that there is some relationship between age, sex, and blood pressure in these differences. A further review is given on p. 107



### 2) Stratification according to the diastolic blood pressure

An analysis of the same differences has also been made according to stratification of the diastolic blood pressure. The results appear in Fig. 6.21. To simplify the presentation only the mean values of the differences between the systolic blood pressure in the sitting position and after 30 minutes rest have been given in these figures. In addition the regression lines are given for each of the groups.

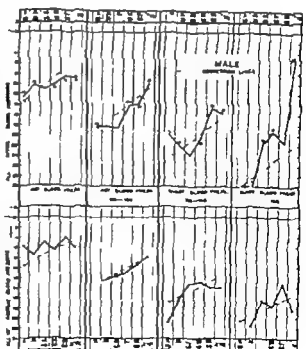


Fig. 6.21 Females & Males. The difference between the systolic and diastolic blood pressure in the sitting position and after resting 30 minutes lying. Mean values. The material is grouped according to the diastolic blood pressure. The regression lines are given. The total number of individuals in each of the groups can be seen from the upper curves.

The differences follow the same linear course that was shown in Fig. 6.20 for the systolic classification of the series.

### Summary and conclusion

The mean values of the systolic blood pressure in 1951-52 in the sitting position show little difference from the 1950 values when classified according to the systolic blood pressure. This is due to the use of the same class-limits as in 1950. However the total number of individuals in each cell is different from that in the 1950 grouping owing to the shift of the individuals from higher to lower blood pressure groups within the same age group.

When classified according to the diastolic blood pressure the mean values of the systolic blood pressure rise steeply with age in all four blood pressure groups except for the women in the group  $\geq 120$  mm Hg (see Fig. 6.19).

The difference between the systolic blood pressure in the sitting and lying

positions and after 30 minutes rest is calculated from the group means, and the material is grouped in two ways by stratification of 1) the systolic and 2) the diastolic blood pressure.

There is a consistent regularity in these differences in both sexes. The differences follow a linear course with a fall in the blood pressure in the groups with high blood pressure. In each of the blood pressure groups it is evident that the fall is greatest in the younger individuals (see Figs. 6.20 & 6.21).

Further the difference in the blood pressure is greatest in men in nearly all the groups.

### The diastolic blood pressure in the sitting position

#### a) The mean values of the diastolic blood pressure

The mean values are shown in Tables 6.16 and 6.17 in the same 24 cells as for the

Table 6.16. Diastolic blood pressure in 1951-52 by age and sex  
Series grouped according to the systolic blood pressure  
Mean, standard error of the mean, and standard deviation

| BP groups<br>1951-52 |        | Age and sex groups |      |       |       |       |       |       |       |       |       |           |       |
|----------------------|--------|--------------------|------|-------|-------|-------|-------|-------|-------|-------|-------|-----------|-------|
|                      |        | 15-29              |      | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | $\geq 70$ |       |
|                      |        | M                  | F    | M     | F     | M     | F     | M     | F     | M     | F     | M         | F     |
| $\leq 14$            | No.    | 67                 | 32   | 56    | 44    | 39    | 33    | 28    | 27    | 20    | 13    | 8         | 10    |
|                      | Mean   | 85.4               | 86.6 | 85.7  | 83.1  | 87.8  | 85.8  | 85.2  | 86.3  | 85.8  | 86.0  | 86.3      | 79.5  |
|                      | S. e.  | 1.1                | 1.2  | 1.0   | 1.3   | 1.2   | 1.2   | 1.5   | 1.2   | 2.1   | 1.9   | 1.4       | 2.9   |
|                      | St. d. | 9.2                | 6.8  | 7.6   | 8.2   | 7.3   | 6.8   | 7.8   | 6.0   | 9.2   | 7.1   | 3.6       | 8.8   |
| 150-175              | No.    | 74                 | 24   | 64    | 59    | 51    | 96    | 40    | 79    | 40    | 45    | 20        | 23    |
|                      | Mean   | 91.7               | 95.2 | 95.2  | 97.7  | 98.2  | 97.9  | 95.9  | 95.9  | 96.0  | 93.7  | 95.3      | 91.3  |
|                      | S. e.  | 0.9                | 1.0  | 1.1   | 1.1   | 1.6   | 0.7   | 1.6   | 0.9   | 1.5   | 0.8   | 2.1       | 1.6   |
|                      | St. d. | 8.0                | 5.0  | 9.2   | 8.0   | 11.4  | 7.0   | 10.2  | 8.0   | 9.2   | 5.5   | 9.2       | 7.7   |
| 180-205              | No.    | 8                  |      | 11    | 14    | 23    | 41    | 26    | 50    | 31    | 58    | 21        | 57    |
|                      | Mean   | 96.3               |      | 102.3 | 107.1 | 107.4 | 106.8 | 109.2 | 106.0 | 101.1 | 103.3 | 103.6     | 101.4 |
|                      | S. e.  | 2.5                |      | 3.3   | 2.6   | 3.8   | 1.3   | 2.5   | 1.4   | 2.2   | 1.0   | 2.7       | 1.2   |
|                      | St. d. | 6.1                |      | 10.6  | 9.2   | 18.7  | 8.4   | 12.7  | 10.0  | 12.0  | 7.6   | 12.1      | 8.9   |
| $\geq 210$           | No.    |                    | 1    | 3     | 5     | 13    | 34    | 14    | 40    | 18    | 41    | 8         | 39    |
|                      | Mean   |                    | 140  | 123.3 | 134.0 | 122.3 | 124.6 | 122.1 | 112.3 | 116.7 | 119.8 | 110.6     | 116.4 |
|                      | S. e.  |                    |      | 14.7  | 15    | 3.1   | 2.3   | 4.7   | 5.7   | 3.2   | 2.0   | 4.1       | 1.9   |
|                      | St. d. |                    |      | 20.7  | 4.9   | 10.7  | 13.3  | 16.8  | 37.3  | 13.3  | 12.8  | 10.8      | 11.4  |

**Table 6.17 Diastolic blood pressure in 1951-52 by age and sex**  
 Series grouped according to the diastolic blood pressure  
 Mean, standard error of the mean, and standard deviation

| BP groups 1951-52 |        | Age and sex groups |      |       |       |       |       |       |       |       |       |       |       |
|-------------------|--------|--------------------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                   |        | 15-29              |      | 30-39 |       | 40-49 |       | 50-59 |       | 60-69 |       | ≥ 70  |       |
|                   |        | M                  | F    | M     | F     | M     | F     | M     | F     | M     | F     | M     | F     |
| ≤ 85              | No.    | 50                 | 14   | 35    | 34    | 19    | 21    | 20    | 19    | 17    | 12    | 10    | 14    |
|                   | Mean   | 78.8               | 79.6 | 79.1  | 79.1  | 76.1  | 80.7  | 77.5  | 81.8  | 77.6  | 82.5  | 81.5  | 78.6  |
|                   | S. e.  | 0.8                | 1.2  | 1.0   | 1.0   | 3.2   | 1.0   | 1.5   | 1.0   | 1.0   | 1.0   | 1.5   | 1.8   |
|                   | St. d. | 5.5                | 4.4  | 6.0   | 5.5   | 13.4  | 4.6   | 6.4   | 4.1   | 8.1   | 3.2   | 4.5   | 6.5   |
| 90-100            | No.    | 92                 | 41   | 85    | 60    | 65    | 105   | 48    | 96    | 55    | 76    | 23    | 62    |
|                   | Mean   | 93.4               | 93.6 | 94.4  | 94.8  | 94.8  | 95.3  | 94.6  | 94.3  | 95.1  | 96.1  | 94.3  | 95.8  |
|                   | S. e.  | 0.5                | 0.7  | 0.5   | 0.6   | 0.7   | 0.5   | 0.7   | 0.5   | 0.6   | 0.5   | 1.1   | 0.6   |
|                   | St. d. | 4.6                | 4.5  | 4.2   | 4.7   | 5.2   | 5.0   | 4.5   | 4.8   | 4.7   | 4.4   | 5.2   | 4.6   |
| 105-115           | No.    | 7                  | 1    | 10    | 20    | 25    | 48    | 25    | 44    | 26    | 42    | 21    | 31    |
|                   | Mean   | 106.4              | 105  | 109.0 | 109.0 | 110.2 | 109.6 | 108.9 | 109.3 | 110.2 | 110.6 | 108.8 | 110.0 |
|                   | S. e.  | 1.1                |      | 1.0   | 0.7   | 0.5   | 0.5   | 0.7   | 0.4   | 0.5   | 0.4   | 0.6   | 0.5   |
|                   | St. d. | 2.8                |      | 3.0   | 3.0   | 2.5   | 2.5   | 3.5   | 2.9   | 2.4   | 2.8   | 2.8   | 2.5   |
| ≥ 120             | No.    |                    | 1    | 4     | 8     | 19    | 50    | 17    | 37    | 11    | 29    | 3     | 22    |
|                   | Mean   |                    | 140  | 127.5 | 128.8 | 125.7 | 129.2 | 127.9 | 127.8 | 125.0 | 126.6 | 128.3 | 125.7 |
|                   | S. e.  |                    |      | 6.5   | 2.8   | 1.8   | 1.5   | 2.2   | 1.4   | 2.3   | 1.7   | 2.7   | 1.5   |
|                   | St. d. |                    |      | 13.0  | 7.4   | 7.1   | 8.1   | 8.7   | 8.4   | 7.4   | 8.9   | 5.1   | 7.0   |

systolic blood pressure. Each group is composed of the same individuals used in the study of the systolic blood pressure. The classification of the material has been done in two ways.

#### 1) Stratification according to the systolic blood pressure

With this classification the mean values in the diastolic blood pressures show an increase with rising blood pressure but there is no increase with age within any of the blood pressure groups. In the group  $\geq 210$  mm Hg on the contrary there is slight fall in both sexes.

The increase with age shown by the mean systolic blood pressure when the material was classified by stratification of the diastolic blood pressure, is not seen for the diastolic blood pressure when the material is analysed according to stratification of the systolic. In other words the

pulse pressure is almost constant with age in the same blood pressure group when the material is stratified according to the systolic blood pressure, in contrast to the findings on the diastolic stratification (see p. 95).

The dispersion expressed by the standard deviation is greatest in both sexes in the highest blood pressure groups, but shows no increase with increasing age. The dispersion in most of the groups is greater in men.

#### 2) Stratification according to the diastolic blood pressure

Owing to the fact that the series has been grouped according to the diastolic blood pressure, the mean values of the diastolic blood pressure are almost the same in the age groups within each of the systolic pressure strata. This is shown in Fig. 6.13 (lower part). There is no sex difference to be seen either



Table 6.18. The difference between the diastolic blood pressure in the sitting and lying position by sex and age  
Series grouped according to the systolic blood pressure

| BP-groups 1951<br>systolic   | Age and sex groups    |                  |                  |                  |                  |                  |                  |                   |                  |                  |                  |                  |                  |
|--|-----------------------|------------------|------------------|------------------|------------------|------------------|------------------|-------------------|------------------|------------------|------------------|------------------|------------------|
|  | 15-29                 |                  | 30-39            |                  | 40-49            |                  | 50-59            |                   | 60-69            |                  | ≥ 70             |                  |                  |
|  | M                     | F                | M                | F                | M                | F                | M                | F                 | M                | F                | M                | F                |                  |
| 145  | No.                   | 67               | 32               | 55               | 44               | 39               | 33               | 28                | 27               | 19               | 15               | 7                | 10               |
|  | Mean ± s.e.<br>St. d. | 6.9 ± 0.5<br>5.2 | 7.8 ± 0.7<br>3.7 | 6.4 ± 0.5<br>4.0 | 4.8 ± 0.7<br>4.5 | 6.7 ± 0.6<br>3.3 | 2.9 ± 0.8<br>4.5 | 5.0 ± 0.7<br>3.7  | 4.4 ± 0.7<br>3.7 | 3.4 ± 0.8<br>3.2 | 2.3 ± 0.8<br>3.1 | 2.9 ± 2.1<br>5.2 | 3.0 ± 1.3<br>4.0 |
| 150-175  | No.                   | 74               | 24               | 64               | 59               | 51               | 96               | 39                | 79               | 41               | 44               | 19               | 23               |
|  | Mean ± s.e.<br>St. d. | 8.5 ± 0.5<br>4.5 | 7.3 ± 0.9<br>4.3 | 7.9 ± 0.5<br>4.2 | 7.0 ± 0.6<br>4.5 | 8.2 ± 0.5<br>3.7 | 7.1 ± 0.8<br>4.5 | 7.1 ± 0.8<br>4.6  | 5.8 ± 0.5<br>4.7 | 7.1 ± 0.8<br>3.1 | 5.3 ± 0.6<br>4.2 | 3.9 ± 1.1<br>4.5 | 5.0 ± 0.9<br>4.1 |
| 180-205  | No.                   | 7                |                  | 11               | 14               | 23               | 41               | 24                | 49               | 31               | 57               | 20               | 30               |
|  | Mean ± s.e.<br>St. d. | 6.2 ± 2.6<br>6.4 |                  | 6.8 ± 1.2<br>3.8 | 4.3 ± 1.2<br>4.1 | 7.2 ± 1.4<br>6.5 | 6.3 ± 0.7<br>4.4 | 8.1 ± 1.2<br>5.5  | 7.0 ± 0.8<br>5.3 | 6.8 ± 0.7<br>3.8 | 7.2 ± 0.8<br>5.9 | 7.3 ± 1.3<br>5.7 | 5.0 ± 0.6<br>4.5 |
| ≥ 210  | No.                   |                  | 1                | 2                | 5                | 13               | 31               | 13                | 39               | 17               | 41               | 8                | 37               |
|  | Mean ± s.e.<br>St. d. |                  | 5.0<br>10.0      |                  | 3.0 ± 1.2<br>2.4 | 8.1 ± 2.0<br>7.1 | 2.6 ± 0.8<br>4.5 | 10.0 ± 1.4<br>4.8 | 7.9 ± 0.8<br>5.2 | 7.4 ± 0.7<br>2.9 | 7.2 ± 0.9<br>5.9 | 6.3 ± 1.8<br>4.7 | 5.9 ± 0.8<br>4.6 |
| The difference between the diastolic blood pressure in the lying position and after reading 30 minutes |                       |                  |                  |                  |                  |                  |                  |                   |                  |                  |                  |                  |                  |
| 145  | No.                   | 67               | 32               | 55               | 44               | 39               | 33               | 28                | 27               | 19               | 15               | 7                | 10               |
|  | Mean ± s.e.<br>St. d. | 3.4 ± 0.7<br>5.3 | 2.8 ± 0.9<br>4.8 | 3.5 ± 0.6<br>4.3 | 3.5 ± 0.8<br>5.1 | 2.4 ± 0.8<br>4.9 | 3.5 ± 0.7<br>4.1 | 3.2 ± 0.9<br>4.8  | 3.9 ± 1.0<br>5.1 | 3.7 ± 1.1<br>4.5 | 5.7 ± 1.6<br>5.9 | 5.0 ± 2.2<br>5.3 | 3.0 ± 1.9<br>5.5 |
| 175  | No.                   | 74               | 24               | 64               | 58               | 51               | 96               | 39                | 79               | 41               | 44               | 19               | 23               |
|  | Mean ± s.e.<br>St. d. | 3.0 ± 0.7<br>6.1 | 6.9 ± 1.4<br>6.5 | 4.8 ± 0.6<br>5.0 | 5.5 ± 0.7<br>5.1 | 4.2 ± 0.8<br>5.7 | 5.0 ± 0.5<br>4.7 | 3.8 ± 1.0<br>6.0  | 3.0 ± 0.6<br>5.4 | 3.3 ± 0.8<br>5.1 | 3.6 ± 0.6<br>3.6 | 4.2 ± 1.0<br>4.3 | 2.4 ± 1.2<br>5.6 |
| 205  | No.                   | 7                |                  | 11               | 14               | 23               | 41               | 24                | 49               | 31               | 37               | 20               | 58               |
|  | Mean ± s.e.<br>St. d. | 4.3 ± 1.3<br>3.1 |                  | 7.7 ± 2.1<br>6.5 | 7.9 ± 1.5<br>5.5 | 4.8 ± 1.5<br>6.8 | 4.8 ± 0.8<br>5.3 | 6.9 ± 1.2<br>5.5  | 5.7 ± 0.8<br>5.2 | 3.4 ± 0.8<br>4.6 | 3.9 ± 0.8<br>5.6 | 3.3 ± 1.1<br>4.8 | 4.1 ± 0.8<br>6.1 |
| 210  | No.                   |                  | 1                | 2                | 5                | 13               | 31               | 13                | 39               | 17               | 41               | 8                | 37               |
|  | Mean ± s.e.<br>St. d. |                  | 5.0<br>10.0      |                  | 5.0 ± 4.5<br>8.9 | 8.1 ± 2.0<br>6.9 | 9.7 ± 1.0<br>5.8 | 3.8 ± 1.3<br>4.4  | 7.2 ± 1.2<br>7.3 | 5.9 ± 1.6<br>6.4 | 4.1 ± 0.9<br>5.8 | 6.9 ± 3.5<br>0.5 | 6.4 ± 1.1<br>6.5 |

Table 6.19. The difference between the diastolic blood pressure: the sitting and lying position by age and sex  
Series grouped according to the diastolic blood pressure

| BP-groups 1951-52<br>diastolic   |              | Age and sex groups |           |            |           |            |            |            |           |           |           |            |           |
|--|--------------|--------------------|-----------|------------|-----------|------------|------------|------------|-----------|-----------|-----------|------------|-----------|
|  |              | 15-29              |           | 30-39      |           | 40-49      |            | 50-59      |           | 60-69     |           | ≥ 70       |           |
|  |              | M                  | F         | M          | F         | M          | F          | M          | F         | M         | F         | M          | F         |
| ≤ 85   | No.          | 50                 | 14        | 34         | 31        | 19         | 21         | 19         | 19        | 15        | 12        | 9          | 11        |
|  | Mean ± s. e. | 4.6 ± 0.7          | 6.1 ± 0.9 | 5.0 ± 0.7  | 5.1 ± 0.6 | 5.9 ± 0.8  | 0.7 ± 0.6  | 5.3 ± 1.2  | 3.9 ± 0.8 | 1.3 ± 0.6 | 2.5 ± 1.0 | 1.1 ± 1.4  | 2.1 ± 0.9 |
|  | St. d.       | 4.5                | 9.5       | 4.2        | 3.4       | 3.5        | 2.8        | 4.9        | 3.5       | 2.2       | 3.2       | 3.9        | 3.1       |
| 90-100   | No.          | 92                 | 41        | 85         | 60        | 63         | 104        | 47         | 90        | 56        | 74        | 22         | 63        |
|  | Mean ± s. e. | 9.1 ± 0.5          | 7.9 ± 0.6 | 7.5 ± 0.4  | 7.2 ± 0.5 | 7.3 ± 0.4  | 6.3 ± 0.4  | 6.1 ± 0.5  | 5.6 ± 0.5 | 6.5 ± 0.6 | 4.8 ± 0.5 | 4.5 ± 1.0  | 4.9 ± 0.6 |
|  | St. d.       | 4.5                | 4.0       | 3.7        | 4.0       | 3.5        | 4.2        | 3.6        | 4.8       | 4.1       | 4.1       | 4.5        | 4.1       |
| 105-115  | No.          | 6                  | 1         | 10         | 20        | 23         | 48         | 23         | 42        | 26        | 42        | 20         | 30        |
|  | Mean ± s. e. | 11.7 ± 1.0         | 15.0      | 11.0 ± 1.6 | 6.8 ± 1.2 | 8.7 ± 1.5  | 7.1 ± 0.8  | 8.5 ± 1.3  | 7.1 ± 0.8 | 8.8 ± 0.9 | 8.1 ± 1.0 | 7.5        | 11        |
|  | St. d.       | 2.1                |           | 4.8        | 5.2       | 6.9        | 5.4        | 6.1        | 5.4       | 4.3       | 6.1       | 4.6        | 3.6       |
| ≥ 120  | No.          |                    | 1         | 3          | 8         | 19         | 31         | 15         | 37        | 11        | 29        | 3          | 21        |
|  | Mean ± s. e. |                    | 5.0       | 10.0       | 9.8 ± 1.2 | 9.2 ± 1.5  | 3.7 ± 0.9  | 11.0 ± 1.0 | 8.6 ± 0.8 | 7.7 ± 1.1 | 8.6 ± 1.2 | 11.7 ± 6.0 | 5.7 ± 1.4 |
|  | St. d.       |                    |           |            | 3.2       | 3.4        | 4.7        | 3.7        | 4.8       | 3.3       | 6.1       | 8.1        | 3.1       |
| The difference between the diastolic blood pressure in lying position and after resting 30 minutes |              |                    |           |            |           |            |            |            |           |           |           |            |           |
| ≤ 85   | No.          | 50                 | 14        | 34         | 31        | 19         | 21         | 19         | 19        | 15        | 12        | 9          | 14        |
|  | Mean ± s. e. | 1.1 ± 0.8          | 1.4 ± 0.8 | 2.6 ± 0.8  | 2.9 ± 0.8 | -0.3 ± 0.7 | 2.6 ± 0.8  | 1.3 ± 1.4  | 2.6 ± 1.1 | 2.7 ± 1.4 | 5.0 ± 1.8 | 3.0 ± 0.8  | 1.1 ± 0.9 |
|  | St. d.       | 3.6                | 2.9       | 4.6        | 4.5       | 3.0        | 3.6        | 0.0        | 4.7       | 5.1       | 6.1       | 4.0        | 3.5       |
| 90-100   | No.          | 92                 | 41        | 85         | 60        | 63         | 104        | 47         | 98        | 56        | 74        | 22         | 63        |
|  | Mean ± s. e. | 4.0 ± 0.4          | 5.6 ± 1.0 | 4.9 ± 0.5  | 5.3 ± 0.7 | 4.4 ± 0.7  | 4.7 ± 0.5  | 4.6 ± 0.8  | 3.3 ± 0.5 | 3.1 ± 0.6 | 3.0 ± 0.6 | 3.6 ± 1.3  | 3.3 ± 0.8 |
|  | St. d.       | 5.1                | 6.4       | 4.6        | 5.5       | 5.5        | 4.7        | 5.1        | 3.2       | 4.6       | 4.4       | 5.8        | 5.9       |
| 105-115  | No.          | 6                  | 1         | 10         | 20        | 23         | 48         | 23         | 42        | 26        | 42        | 20         | 30        |
|  | Mean ± s. e. | 9.2 ± 3.0          | 5.0       | 5.5 ± 1.6  | 7.0 ± 1.1 | 4.6 ± 1.3  | 5.4 ± 0.7  | 4.6 ± 1.1  | 6.1 ± 0.9 | 5.2 ± 1.2 | 4.2 ± 0.9 | 6.5 ± 1.3  | 5.7 ± 1.3 |
|  | St. d.       | 6.6                |           | 4.7        | 4.5       | 6.0        | 5.0        | 5.0        | 5.6       | 3.7       | 5.8       | 5.7        | 6.8       |
| ≥ 120  | No.          |                    | 1         | 3          | 8         | 19         | 28         | 15         | 37        | 11        | 29        | 3          | 21        |
|  | Mean ± s. e. |                    | 5.0       | 11.7 ± 7.2 | 7.5 ± 5.9 | 7.4 ± 1.8  | 10.4 ± 1.1 | 6.7 ± 1.5  | 7.6 ± 1.2 | 5.5 ± 1.8 | 5.9 ± 1.0 | 6.7 ± 4.4  | 7.6 ± 1.4 |
|  | St. d.       |                    |           | 10.2       | 8.6       | 7.8        | 5.5        | 5.6        | 7.2       | 3.7       | 5.5       | 6.2        | 6.1       |



Table 6.20. The difference between the systolic blood pressure measured in the sitting position and after resting 30 minutes in the lying position  
The material stratified according to diastolic blood pressure Mean values  
Observed and calculated differences

| Diastolic<br>BP<br>1951-52 | Differ-<br>ences | Age groups |       |       |       |       |      |
|----------------------------|------------------|------------|-------|-------|-------|-------|------|
|                            |                  | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 |
| F e m a l e                |                  |            |       |       |       |       |      |
| ≤ 85                       | No.              | 14         | 34    | 1     | 19    | 12    | 14   |
|                            | Calc.            | 14.7       | 13.1  | 11.5  | 9.9   | 8.3   | 6.7  |
|                            | Obs.             | 9.3        | 9.8   | 10.5  | 12.5  | 8.4   | 10.4 |
| 90-100                     | No.              | 41         | 60    | 104   | 96    | 74    | 63   |
|                            | Calc.            | 18.2       | 16.6  | 15.0  | 13.4  | 11.8  | 10.2 |
|                            | Obs.             | 18.3       | 18.2  | 17.0  | 14.0  | 9.5   | 11.3 |
| 105-115                    | No.              | 1          | 20    | 48    | 4     | 4     | 30   |
|                            | Calc.            | 21.7       | 20.1  | 18.5  | 16.9  | 15.3  | 13.7 |
|                            | Obs.             | 33.0       | 18.3  | 18.8  | 15.0  | 14.2  | 12.0 |
| ≥ 120                      | No.              | 1          | 8     | 28    | 37    | 29    | 21   |
|                            | Calc.            | 25.2       | 23.6  | 22.0  | 20.4  | 18.8  | 17.2 |
|                            | Obs.             | 23.0       | 21.3  | 24.2  | 20.7  | 18.4  | 17.6 |

$$y = 3.50 \text{ BP} - 1.60 \text{ A} + 12.81$$

Multiple correlation coefficient = 0.88

|         |       |       |       |       |       |       |       |
|---------|-------|-------|-------|-------|-------|-------|-------|
| Male    |       |       |       |       |       |       |       |
| ≤ 85    | No.   | 50    | 34    | 19    | 19    | 15    | 9     |
|         | Calc. | 13.49 | 11.91 | 10.33 | 8.75  | 7.17  | 5.59  |
|         | Obs.  | 12.6  | 10.4  | 11.1  | 10.2  | 8.6   | 8.9   |
| 90-100  | No.   | 92    | 85    | 63    | 47    | 36    | 22    |
|         | Calc. | 18.92 | 17.34 | 15.76 | 14.18 | 12.60 | 11.02 |
|         | Obs.  | 18.4  | 18.4  | 18.7  | 14.5  | 13.9  | 10.5  |
| 105-115 | No.   | 6     | 10    | 23    | 23    | 26    | 20    |
|         | Calc. | 24.35 | 22.77 | 21.19 | 19.61 | 18.03 | 16.45 |
|         | Obs.  | 20.0  | 22.5  | 23.9  | 20.6  | 14.8  | 15.8  |
| ≥ 120   | No.   | 3     | 3     | 19    | 15    | 11    | 3     |
|         | Calc. | 29.78 | 28.20 | 26.62 | 25.04 | 23.46 | 21.88 |
|         | Obs.  |       | 30.0  | 21.5  | 19.3  | 21.3  | 5.0   |

$$y = 4.12 \text{ BP} - 1.38 \text{ A} + 11.78$$

Multiple correlation coefficient = 0.86

The difference between the diastolic blood pressure in the sitting and lying positions and after 30 minutes rest is greater in the higher blood pressure groups and more marked when the series is grouped according to the diastolic blood

pressure. In both classifications the fall in the diastolic blood pressure is greatest in the young.

All groups show the sex differences described for the systolic blood pressure.

The differences in the diastolic blood

**Conclusion** The linear relationship of the blood pressure differences to age and blood pressure is described. The analyses show that even though the variation among the

different individuals is great, a definite trend appears when the calculations are based upon the mean values of the groups.

## The results of the blood pressure measurements applied to the Bergen series

### The frequency distribution of the systolic and diastolic blood pressure sitting, lying, and after 30 minutes rest

The calculations presented in this chapter show that in spite of great individual variations there is a definite pattern present in this random sample of the Bergen series when the individuals are grouped according to blood pressure and age.

Therefore it is reasonable to apply the findings from these blood pressure measurements to the Bergen series. This can be done by using the ratios given in Table 5.3. These ratios indicate the number of individuals in the primary series (Bergen series, group I) represented by one individual in this series. On the basis of these ratios one can construct a theoretical frequency distribution of the systolic and diastolic blood pressure measured sitting, lying and after 30 minutes rest.

These calculations are illustrated in Fig 6.22

The diagram shows the variability of the systolic and diastolic blood pressures in both sexes, when applied to the Bergen series. The curves illustrate the way in which the systolic and diastolic blood pressures tend to fall from the sitting to the lying position, with a further fall after 30 minutes rest. The mode also shows a fall in the systolic blood pressure in both sexes, while it does not show any fall in the diastolic pressure in women. Further it can be seen that the curves become higher and narrower as the scatter of the blood pressure values decreases.

The object of these frequency distribution curves is only to give a picture of the variability of the blood pressure approximately as it would be in the population sample. The difference in the variability of the blood pressure that was noticed in the younger and older individuals is not apparent in this presentation.

## Discussion

The purpose of the calculations presented in this chapter has been to throw light on the variability of the blood pressure in this grouped series.

In the first part of the chapter the calculations are made on the basis of a stratification of the systolic blood pressure in 1950 and the calculations have been done to illustrate

- 1) The difference in the group means in the 1950 and the 1951-52 measurements.

- 2) The difference in every single individual in each of the groups in both sexes.

In the second part of the chapter the calculations are made on the basis of a classification of the blood pressure in 1951-52. The calculations have been made in part by a stratification of the systolic, and in part by the diastolic blood pressure.

It is well known that the blood pressure varies and that the variability is as a rule greatest in those with raised blood pressure.

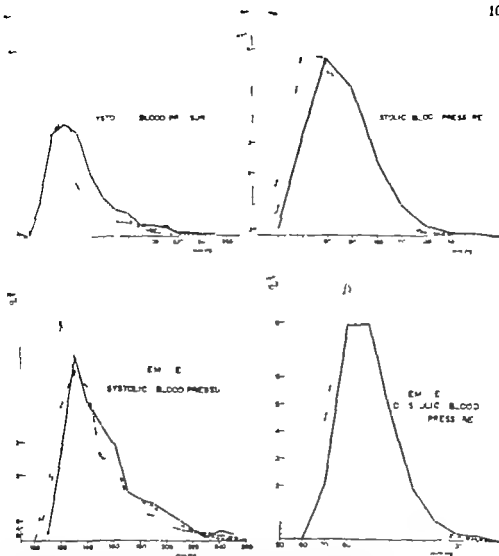


Fig 6.22. Systolic and diastolic blood pressures. Frequency distribution curves of theoretical population based upon the study group. The curves show the blood pressure

- in sitting position
- - - in lying position
- after 30 minutes rest.

Hardly an individual can be found in whom the blood pressure is fixed at a constant level. Certainly a few cases of serious hypertensive disease are to be found in which the blood pressure is more or less fixed, but in general, hypertension is characterized by marked variability

Thus Ayman (11) points out that variability is the outstanding characteristic of the blood pressure itself and the disease itself.

The variability seen depends to a great extent on the total number of readings and how frequently the measurements are taken. In every individual fluctuations can

be noticed from minute to minute with repeated readings. In the above mentioned study by Diehl & Lees (50) there was a continuous fall with readings taken every fifth minute for one hour in the sitting position. This fall was greatest in the first two 5-minute readings. The fall in hypertensives is more pronounced after a shorter rest period than it is in normal individuals. Ayman (11) found a considerable fall with measurements taken every 5th minute during 45 minutes rest in the sitting position. This percentage fall was as pronounced for the diastolic as for the systolic blood pressure. The hypertensives with marked arteriosclerosis also showed wide fluctuations in the diastolic blood pressure.

Veale *et al* (229) measured the blood pressure in 370 patients attending hospital clinics unlikely to attract patients with unusual blood pressures. It was found with repeated measurements at half minute intervals, the doctor being present throughout, that the blood pressure fell much more than it did when the doctors entered and took only a few measurements after the patient had been resting.

Considerable variations have been noticed during the course of the 24 hours. Many have studied these diurnal variations and all have noticed a fall during sleep. Thus, in individuals with normal and with raised blood pressure Müller (161) found that the fall was greatest in the hypertensive patients and proportional to the severity of the hypertension. Mueller & Brown (160) found pronounced variations over the 24 hours from hourly measurements, and the variation was greatest in those with hypertension.

Hammarström (93) studied the spontaneous variability by means of 24-hour readings, amylal nitrite, and cold pressor tests, on bedridden patients classified according to retinal changes. The rest in bed during the first days after admission caused a greater drop in blood pressure than further bed rest. In patients with encephalopathy the mean values of the 24-hour readings after 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, 21st, 22nd, 23rd, 24th, 25th, 26th, 27th, 28th, 29th, 30th, 31st, 32nd, 33rd, 34th, 35th, 36th, 37th, 38th, 39th, 40th, 41st, 42nd, 43rd, 44th, 45th, 46th, 47th, 48th, 49th, 50th, 51st, 52nd, 53rd, 54th, 55th, 56th, 57th, 58th, 59th, 60th, 61st, 62nd, 63rd, 64th, 65th, 66th, 67th, 68th, 69th, 70th, 71st, 72nd, 73rd, 74th, 75th, 76th, 77th, 78th, 79th, 80th, 81st, 82nd, 83rd, 84th, 85th, 86th, 87th, 88th, 89th, 90th, 91st, 92nd, 93rd, 94th, 95th, 96th, 97th, 98th, 99th, 100th, 101st, 102nd, 103rd, 104th, 105th, 106th, 107th, 108th, 109th, 110th, 111th, 112th, 113th, 114th, 115th, 116th, 117th, 118th, 119th, 120th, 121st, 122nd, 123rd, 124th, 125th, 126th, 127th, 128th, 129th, 130th, 131st, 132nd, 133rd, 134th, 135th, 136th, 137th, 138th, 139th, 140th, 141st, 142nd, 143rd, 144th, 145th, 146th, 147th, 148th, 149th, 150th, 151st, 152nd, 153rd, 154th, 155th, 156th, 157th, 158th, 159th, 160th, 161st, 162nd, 163rd, 164th, 165th, 166th, 167th, 168th, 169th, 170th, 171st, 172nd, 173rd, 174th, 175th, 176th, 177th, 178th, 179th, 180th, 181st, 182nd, 183rd, 184th, 185th, 186th, 187th, 188th, 189th, 190th, 191st, 192nd, 193rd, 194th, 195th, 196th, 197th, 198th, 199th, 200th, 201st, 202nd, 203rd, 204th, 205th, 206th, 207th, 208th, 209th, 210th, 211st, 212nd, 213th, 214th, 215th, 216th, 217th, 218th, 219th, 220th, 221st, 222nd, 223rd, 224th, 225th, 226th, 227th, 228th, 229th, 230th, 231st, 232nd, 233rd, 234th, 235th, 236th, 237th, 238th, 239th, 240th, 241st, 242nd, 243rd, 244th, 245th, 246th, 247th, 248th, 249th, 250th, 251st, 252nd, 253rd, 254th, 255th, 256th, 257th, 258th, 259th, 260th, 261st, 262nd, 263rd, 264th, 265th, 266th, 267th, 268th, 269th, 270th, 271st, 272nd, 273rd, 274th, 275th, 276th, 277th, 278th, 279th, 280th, 281st, 282nd, 283rd, 284th, 285th, 286th, 287th, 288th, 289th, 290th, 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measurements were taken over a period of 3 weeks with the measurements of the series taken with readings every 5th minute 6 times in all in each series. The measurements were repeated over 17 week days in all. The results showed that the blood pressure varied considerably from day to day. The conclusion was that no single reading or group of readings obtained on a single day as performed in this study could serve as an index of blood pressure variability over the three week period of this study.

It is important to be aware of these relationships when evaluating the results of this series. It must, however, be remembered that the method of taking the blood pressure is not identical with that used by Glock and co-workers. As the lowest blood pressure obtained with each of the three readings has been noted consistently in this series some of the fluctuations will be hidden.

The analysis in this series confirms that there are considerable fluctuations in the casual blood pressure. The variability in each individual is evident from the histograms when analysing the differences both between the 1950 and 1951-52 measurements, between the sitting and lying positions, and after 30 minutes' rest.

The variability is apparently more marked in the individuals belonging to groups with high blood pressure. This is seen when considering the standard deviation, but the coefficient of variation does not always verify this. Thus the coefficient of variation of the systolic blood pressure in 1950 is nearly the same in the blood pressure groups  $\leq 85$  mm as in the  $\geq 210$  mm groups, and these two groups show a higher coefficient of variation than the two middle blood pressure groups. This is what one would expect as the two middle blood pressure groups have a fixed group interval of 30 mm, while the groups  $\leq 85$  and  $\geq 210$  mm are open. The coefficient of variation is higher in nearly all corresponding groups in the 1951-52 frequency distribution of the

systolic blood pressure than in the 1950 frequency distribution. This is also what one would expect, as the 1950 frequency distribution is broken up into subgroups on the basis of the level of the systolic blood pressure (see Fig 6.1) while the blood pressure in 1951-52 shows an almost symmetrical distribution. The 1951-52 frequency distribution does not show any systematic difference in the coefficient of variation between the different blood pressure strata. The diastolic blood pressure, on the other hand, shows a slightly higher coefficient of variation in the highest blood pressure group both in the 1950 and in the 1951-52 distributions in both sexes.

When adding together the differences in systolic and diastolic blood pressure between the 1950 and 1951-52 readings in all the individuals the mean values give a characteristic trend as is shown in the many diagrams.

Hamilton and co-workers (89) measured the blood pressure a second time in 180 of the 2,031 subjects included in their population sample (see p. 21). It appeared that in each sex the difference between the two readings increased with the height of the original blood pressure. It could also be shown that the difference increased with age.

The present study was carried out from 9 months to 9 years after the Bergen series (group I). In spite of differences in methods and facilities, and the rather long interval, the same tendency was observed. The mean values of the systolic blood pressure decreased in the groups with high, and increased in the groups with low systolic blood pressure, according to age.

This tendency was also noticed by Comstock (44) in his epidemiological study (see pp. 21 and 69). Here the blood pressure readings were taken after a very short interval (40-80 hours later). When the deviations of the systolic and diastolic blood pressures were studied in relation to the height of the initial reading it was apparent that people with high initial pressures tended to show the greatest



subsequent decrease, while those with the lowest pressures tended to show a slight increase at the subsequent determination. Comstock points out that the tendency for persons with blood pressures at the extremes of the frequency distributions to have values on subsequent examinations which are closer to the mean values for the entire population is merely another example of regression towards the mean first noted by Galton in his studies on heredity in 1877.

As far as is known to the author there are very few who have investigated the variability of the blood pressure in a random series of the population. Many authors have studied the variability by repeated measurements in the hypertensive, but the majority of series are more or less selective both with regard to age and to blood pressure. It is only when one works with a grouped series of individuals of different ages and with different blood pressure that this tendency of regression towards the mean becomes apparent.

Several times in this chapter it has been mentioned that 6 young women have shown findings deviating from those in the remainder with an increase in the systolic as well as the diastolic blood pressure and pulse pressure. In these groups no percentage selection of the population was made, as all the individuals (100 %) in the Bergen series were examined.

The one individual (15-29) with a systolic blood pressure of 180 mm Hg (1950 series) suffered from unilateral hypertension. In the group 30-39 with systolic blood pressure  $\geq 210$  4 showed renal manifestations, 3 of whom had chronic nephritis, and one presented the typical picture of the malignant phase of essential hypertension. The 5th individual had diabetes mellitus without renal complications judged by routine kidney function tests. Four of the individuals in the 30-39 year group showed signs of a progressive illness and these 4 died a few years afterwards.

However this series is made up of such

a small number of individuals with renal disease and secondary hypertension from other causes that no general conclusions can be drawn as to the deviations of the blood pressure except in the small group mentioned above. This finding agrees well with that of Hammarström (93) who concluded that there was no significant difference between blood pressure level and variability in essential hypertension and hypertensive renal disease indicating that a study of blood pressure could elucidate the aetiology of hypertensive disease.

There are certainly several individuals to be found in the series who also show an increase in the blood pressure from 1950 to 1951-52. A closer study of the frequency distribution curves verifies this. However these cases do not have any marked influence on the trend or the linear course of the mean values of the groups concerned, as shown in Fig. 6.8.

In the second part of this chapter the difference between the blood pressure in the sitting and lying positions and during the 30 minutes rest period has been studied. When analysing the mean values in the groups a fall in the blood pressure is evident. This fall shows a considerable regularity dependent on age, sex, and blood pressure.

It is evident that the fall in the blood pressure is greatest in the groups with high blood pressure. There is also an unambiguous sex difference in all the measurements in the different positions. The men in nearly all the groups, show greater lability than the women. The difference is greatest in the groups with high blood pressure. This applies both to the systolic and the diastolic blood pressure, whether one measures the difference from the sitting to the lying position or after 30 minutes rest.

This finding is rather interesting and cannot be found in the literature elsewhere. In the above-mentioned study of Veale *et al.* (229) it can be seen from the curves that the fall in the blood pressure was greatest among the older women.

The findings in this study also reveal a marked relationship to age, as the lability is greatest in the younger. This influence of age appears to be quite linear for both the systolic and the diastolic blood pressure. Veale *et al.* (229) found that the fall of the blood pressure was greatest among the oldest the height of the blood pressure, however was higher in this age group compared with the younger.

The variation in the difference between the blood pressure in the sitting position and after 30 minutes rest has been described as a function of age and blood pressure for each sex separately giving a linear relationship to age and blood pressure. The implication of this finding can not be stated with certainty though it seems reasonable to relate the effect of ageing to the morphological and physiological changes of the circulatory system. In the groups with high blood pressure the fluctuations increase with increasing blood pressure, especially among the young possibly due to the relaxation of vascular tone (vasoconstrictor mechanisms) during the resting period. The elasticity of the aorta, great vessels and the muscular arteries decreases in athero- and arteriosclerosis, the prevalence of which is known to increase with age. It is therefore not unlikely that the variability of the systolic and diastolic blood pressure is smaller

among the old and greater among the young.

The lability of the blood pressure with the relatively large fall after 30 minutes rest indicates that one should be careful of interpreting a somewhat high casual blood pressure as pathological. The findings demand that the norms and limits of pathological and 'normal' blood pressure should not be too fixed. One must not set up rigid standards of normality which in reality are non-existent. It is also very important to be aware of this variability when evaluating a therapeutic trial.

The calculations of the blood pressure that have been made in this chapter show up quite interesting trends concerning the dynamics of the blood pressure. There are still many questions to be raised concerning the lability of the blood pressure. Among others the influence of excess weight and emotional factors has to be taken into account. These questions will not be answered in this monograph.

Finally in the pages that follow an attempt will be made to evaluate the influence of this lability on the clinical symptoms and findings. Fishberg (69) states that the study of blood pressure is only one method of examination, and its results can be interpreted rationally only in the light of the complete clinical picture.

## CHAPTER VII

# Cardiac signs and symptoms with special reference to the influence of age and blood pressure

### Definition

#### Survey of the literature

Hypertension affects the heart in two ways. Fishberg (69) states that the heart is confronted by two sources of danger in increased work due to high blood pressure and impairment of blood supply resulting from the coronary arteriosclerosis that almost inevitably develops.

The raised blood pressure causes an increase in the work of the heart and this will sooner or later lead to increasing *left ventricular hypertrophy*. Histological investigation shows that hypertrophy involves every single muscle fibre of the left ventricle, affecting all elements of the muscle cell. On the other hand no increase in the total number of muscle fibres is found.

There seems to be a connection between the hypertrophy and the height of the blood pressure. Experimental investigation on animals, made by Pickering & Prinzmetal (180) among others, shows this relationship to be approximately proportional. This hypertrophy affects mainly the left ventricle.

Clinically and radiologically it is often difficult to determine how much is due to the hypertrophy itself and how much depends on a combination of hypertrophy and dilatation.

On the other hand the pathologist can determine the degree of hypertrophy by weighing the heart, and the weight is considered to be the best index of the hypertrophy. In many pathologico-anato-

mical studies a distinct correlation is to be found between hypertrophy and the severity of the hypertension. Thus Stein & Barnes (220) investigated 111 individuals (65 men and 46 women) all of whom had earlier shown a normal blood pressure (under 140/90) on many occasions, but in whom hypertension had later developed. However no details of age are given. The series was grouped according to Keith and Wagener's classification, and hypertrophy was judged from the heart weight reckoned as a percentage of the normal heart weight. Hypertrophy turned out to be 49.5 % in group 1 and 36.9 % in group 2, rising to 60.1 % in group 3 and 87.6 % in group 4. No relationship was found between the degree of hypertrophy and the duration of the hypertension.

Similar results were obtained by Smith, Odel & Kernohan (212). Their series consists of 576 cases of primary hypertension selected from 2 650 consecutive cases of hypertension and grouped according to Keith & Wagener's classification with 100 individuals in each of groups 1, 2 and 4 and 75 in group 3. A correlation was found between the heart weight and the severity of hypertension, but no correlation between the heart weight and the duration of the hypertension.

The second point in the pathogenesis of hypertensive heart disease is the *development of coronary sclerosis*.

This problem has interested many pathologists. Thus Bell & Clawson (19)

in a clinical and pathologico-anatomical investigation comprising 420 patients with primary hypertension found that coronary sclerosis was more common and more marked in those who were hypertensive than in the normotensive. Certain types of arteriosclerosis (in the coronary and the smaller cerebral arteries) show a close relationship to hypertension, but sclerosis in the aorta and the peripheral arteries does not show any definite relationship to hypertension. Of the individuals in their series 74 % were over 50 years of age. The sex distribution was somewhat uneven with a preponderance of men (36 %). Hypertension was defined as a systolic blood pressure of 150 mm or higher or as considerable left ventricular hypertrophy which could not be explained by any other disease.

Davis & Klainer (46) have also examined the connection between hypertension and arteriosclerosis in several publications. The degree of the coronary atherosclerosis was correlated to the level of the blood pressure in a selected series comprising 137 patients with a blood pressure consistently higher than 150 mm, systolic and a diastolic of over 90 mm, together with a control series of 324 individuals. The patients with hypertension showed more coronary sclerosis than the controls, the difference in incidence being around 76 %. The difference was most marked before the age of 50 years. More coronary disease developed in men without hypertension than in the women, especially before the age of 60. Essential hypertension increased the incidence of coronary atherosclerosis proportionately in both sexes. In spite of the higher incidence of hypertension in women the degree of the coronary atherosclerosis was significantly lower. But even though the frequency of coronary sclerosis is relatively high in essential hypertension, it appears that the incidence is not greater in those with severe hypertension (as shown both by the general blood pressure level during life and by the extent of cardiac hyper-

trophy at necropsy) than in those with mild degrees of hypertension.

Several authors have noticed that the reduction in the coronary circulation that follows arteriosclerosis leads to hypertrophy of the heart. Davis & Blumgart (45) have investigated the degree of hypertrophy in relation to coronary sclerosis and heart failure. All cases with hypertension syphilis, rheumatic heart disease and anaemia were eliminated beforehand. There was little or no hypertrophy of the heart with minor degrees of arteriosclerosis in the coronary vessels, but with advanced arteriosclerosis they found a slight or moderate degree of hypertrophy presumably due to impaired nutrition of the muscle fibres which causes them to undergo stretching and consequent hypertrophy. A considerable increase in the heart weight was found in cases of congestive heart failure. The authors conclude that these results support the injury theory of Horvath (101) Albrecht (3) and Eyster (67) on the causation of cardiac hypertrophy rather than the widely held 'work-hypertrophy' theory.

Hypertrophy of the heart is thus a characteristic finding in hypertension but the pathogenesis of this hypertrophy is somewhat obscure.

Some of the pathologico-anatomical investigations have been referred to here as they are of importance later in this thesis (p. 134). When evaluating these investigations one must be aware that few of the authors have stated whether the death was due to a cardiac cause or whether the cardiac findings at autopsy were secondary. In addition the criteria for hypertension are somewhat indistinct in several of the publications. Some authors give a fixed borderline for the blood pressure regardless of age and sex. Furthermore, there is a definite selection in several series as regards sex.

Clinically it is of great importance to estimate the size of the heart. A rough estimation can be made by locating the pex beat. A more exact estimate can be

obtained by radiography and electrocardiography. One should be aware that clinically, radiologically and electrocardiographically it may be difficult to determine how much of the demonstrable enlargement of the heart is due to hypertrophy and how much to dilatation. An accurate assessment of hypertrophy alone can only be obtained from pathologico-anatomical investigations and by weighing the heart.

### Signs and symptoms

According to Fishberg (69) one can distinguish 3 stages in the course of hypertensive disease and in the natural history of heart failure

- 1 Cardiac compensation.
- 2 Isolated left ventricular failure.
- 3 Combined left and right-sided failure.

These three stages are not always sharply distinguishable from each other and the change-over is often imperceptible. Generally the course is long drawn out and the compensated state can continue for years or even decades.

The subjective symptoms depend on the degree of heart failure. In the compensated state no symptoms manifest themselves; in some cases there may be slight dyspnoea on exertion.

These symptoms appear first when the symptoms of left ventricular failure show themselves. The symptoms can occur suddenly and progress rapidly but in most cases the development takes place gradually over many years. Besides dyspnoea on exertion it is paroxysmal attacks of dyspnoea, occurring during rest, that are characteristic of this stage. The paroxysms can be of all degrees of severity from slight disturbances during sleep to severe attacks of cardiac asthma and lung oedema.

Sooner or later symptoms of right heart failure appear with more or less pronounced dyspnoea, increased venous pressure, cyanosis, oedema, congestion of the

liver and lungs and eventually transudates. Enlargement of the heart is also characteristic of serious cases of heart failure.

The occurrence of arrhythmia is relatively uncommon in the compensated state or in uncomplicated left ventricular failure, but it generally occurs in the later stages.

As has been mentioned earlier there are many indications that coronary sclerosis and coronary disease develop to a greater extent in those who are hypertensive than in those who are normotensive. The appearance of the symptom angina pectoris points to the diagnosis of coronary sclerosis. Hypertension *per se* does not cause angina pectoris. Some findings indicate that the heart in hypertension may be predisposed to attacks of angina pectoris with less pronounced coronary sclerosis than in the case in normotensives. Davis & Klainer (46) investigated this relationship in one of their publications. In a series consisting of 40 cases of angina pectoris with hypertension and 21 cases of angina pectoris without hypertension, they found that an extreme degree of coronary disease involving two or more major arteries was present in 95 % of the patients without hypertension but in only 39 % of the patients with hypertension. The incidence of myocardial infarction was correspondingly much higher in the patients without hypertension. Angina pectoris occurred in cases of hypertension which had much less coronary disease than was found in the patients without hypertension. The authors conclude that thus there are two factors present in patients with hypertension whose angina pectoris is associated with lesser degrees of coronary sclerosis (1) cardiac hypertrophy and (2) increased cardiac work.

Fishberg (69) states that his experience is the same. Similarly Pickering (176) states that it seems probable that a lesser degree of coronary disease produces a given degree of ischaemia in the hypertrophied heart of subjects with hypertension than in the smaller hearts of subjects with normal pressures.

Coronary thrombosis is an ever-present danger in individuals with a combination of hypertension and coronary disease, even among the younger ones.

## Prevalence

A survey of the hypertensive heart diseases has been given above from the pathologico-anatomical and certain clinical studies. In many textbooks and monographs clear and instructive accounts of the heart in hypertension are to be found. Examples are those of Fahr (68) Fishberg (69) Friedberg (76) Pickering (176) and White (233) but one does not find detailed information on the frequency of the different symptoms and objective findings in the works of these authors. It is therefore necessary to go through the literature more closely with this point in mind.

The best and most complete information on the frequency of the different cardiac symptoms and signs is to be found in the follow-up studies. A very extensive literature exists in this field. In his monograph, Mathisen (144) has grouped the best known follow up studies under 3 main headings

1. Studies on those who are presumably healthy
2. Studies on out patients.
3. Studies on hospital patients.

This grouping appears to be rational and is also used in this review of the literature.

In the studies that can be placed in the first group there are very few details of the frequency of the different symptoms and signs on the other hand, one finds that the causes of death are given.

Thus in Rogers & Hunter's (194-195) investigations on applicants for life insurance one finds that a cardiac type of death occurred in 33 % compared to 15 % of renal and cerebral deaths. In Levy White Stroud & Hillman's (126) investigations of 22 741 army officers (see pp. 132 and 143) sustained hypertension developed

in 1 472 (6.5 %) 108 died of cardiovascular renal conditions while in service. Cardiac disorders caused death in 72 (67 %) and coronary heart disease in 47 (43 %) while cerebral hemorrhage killed 24 (22 %) and renal disease 12 (11 %)

Both these series are selective with a considerable excess of men.

The studies in group 2 give better information on the cardiac findings than the first group. One of the best known is Janeway's (105) classic work of 1913 comprising 458 patients (307 men and 151 women) with permanent hypertension (lower borderline 165 mm systolic) selected from his private patients. The age distribution showed that between 80-90 % belonged to the 40-69 year age group. In one 9-year observation period 212 (46.3 %) died, considerably more men (53.1 %) than women (52.5 %). The cardiac are among the most frequent causes of death thus 52.6 % died of gradually increasing heart failure, while uraemia and cerebral deaths together accounted for 40.8 %. Cardiac symptoms occurred very frequently in the 246 survivors for instance, dyspnoea in 58.2 % lung oedema 1.2 % angina pectoris in 17 % and peripheral oedema in 10.9 %. The series was further investigated to find the incidence of hypertrophy of the heart (as judged by palpation and localization of the apex beat) Among those who died moderate hypertrophy was found in 50% and marked hypertrophy in 23 % while the survivors showed 34 % and 8 % respectively Janeway further investigated the auscultatory findings also (see p. 163) and the incidence of peripheral arteriosclerosis.

Paullin, Bowcock & Woods (171) series from 1926 comprising 500 private patients with essential hypertension (systolic blood pressure of 160 mm Hg or more or diastolic 100 mm or more) was followed for an average of 8 years. The most common visceral manifestations were concerned with the heart (27.4 %). Complications in the central nervous system occurred

obtained by radiography and electrocardiography. One should be aware that clinically radiologically and electrocardiographically it may be difficult to determine how much of the demonstrable enlargement of the heart is due to hypertrophy and how much to dilatation. An accurate assessment of hypertrophy alone can only be obtained from pathologico-anatomical investigations and by weighing the heart.

### Signs and symptoms

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signs of myocardial damage were found in 18 (36 %) in two of whom the changes took place immediately before death the average observation period was 6½ years. The authors conclude that the series is selective but shows that a long life is not unusual. The majority had well established hypertension of shorter or longer duration before the period of observation. The initial level of the blood pressure does not seem to be associated with either the symptoms, the rate of progression or with the subsequent development of major cardiovascular complications.

In Bechgaard's well known follow-up study (17) the cardiac manifestations were investigated more closely. The following cardiac manifestations were found at the first investigation: dyspnoea on exertion was the most frequent complaint and occurred in 36.5 % of the men and 41 % of the women. Few people showed definite heart failure, and dyspnoea at rest occurred in only 1.3 % of the men and 8.4 % of the women. Cardiac oedema was present in 5.2 % and 9.2 % respectively and lung oedema in 2.6 % and 6.4 %. Palpitations were found more commonly in women (30.8 %) than in men (22 %). Angina pectoris was commoner in men (6.1 % to 2.9 %) while the frequency of cardiac pain was about equal in both sexes (12.8 & 15.4 %). There were no symptoms in 42 %. By the second examination the frequency of symptoms had on the whole increased with a corresponding fall in the number of symptom-free cases (32 %). The electrocardiographic and radiological findings were also studied in this series.

Frant & Groen's series from 1950 (74) consists of 418 patients referred for out patient investigation and followed up 8-9 years later. All of them showed a blood pressure of 155 mm systolic and 100 mm diastolic or over at the first investigation. The age distribution showed a maximum between 50-59 years, and the series was composed of twice as many women (276) as men (142).

Cardiac complications occurred in more than half of them, as 80 out of 125 men and 137 out of 222 women with essential hypertension showed objective signs of organic heart disease. Of these 45 % of the men and 29 % of the women died during the observation period. Dilatation of the heart combined with symptoms of failure (cyanosis, oedema, ascites, gallop rhythm and cardiac asthma or angina pectoris) resulted in a considerable increase in the death rate. 61 % of the men and 41 % of the women died in this way. In this series, too, cardiac deaths were the most common (41 %) while cancer occurred in 16 % uraemia in 15 % and apoplexy in 8.6 %.

In 1954 Mathisen (144) published a series consisting in part of ambulant and in part of hospitalized patients, 111 men and 178 women 290 in all. The individuals were all under 46 years old and were selected, as they had a systolic blood pressure of 160 mm or more or a diastolic of 95 mm or more. Follow-up was carried out 9-10 years later and all the individuals showing secondary hypertension were eliminated.

In contrast to the majority of follow-up studies Mathisen found that cerebral complications were the most frequent cause of death (59.1 %) while cardiac causes occurred in 25.8 % and renal in 9.3 %. At the first examination dyspnoea on exertion was found in 30 % of the men and 45 % of the women, dyspnoea at rest was very rare (6 individuals). Oedema as a sign of heart failure was noticed in 13 % of the women and 3.5 % of the men. Systolic and diastolic murmurs were present respectively in 33.8 % and 3.1 % of the series, but no other details of these murmurs are given. Accentuation of the second aortic sound was found in 25.5 %; all the auscultatory findings showed about the same distribution in men as in women. Definite enlargement of the heart was shown radiologically in 12 women and 6 men, but this investigation was only done on half the series.



In 1955 Perera (174) published a series of 500 patients with hypertensive vascular disease. One hundred and fifty were followed from before onset of hypertension until their death and 350 were followed from an uncomplicated hypertensive phase until death. The majority of the individuals were out patients. The cases were examined at least once a year. Those who showed a diastolic blood pressure of 90 mm or higher on repeated casual measurements were considered to be hypertensive, after the exclusion of those with transient rises of blood pressure. The ratio of men to women was 1:2, the average age of the 150 patients at the start of the illness was 32 years, and the average length of life 20 years. Cardiac complications were the most common with congestive failure in 50 %, angina pectoris in 16 %, and myocardial infarction in 8 %. Radiologically demonstrable cardiac enlargement was found in 74 % and electrocardiographic signs of hypertrophy were present in 39 %. The cause of death was congestive failure as the primary event in 22 %, but as a contributing factor in 38 %. Cerebral vascular accidents occurred in 9 %, myocardial infarction and renal insufficiency in 6 %. However the cause of death could not be established in 43 %.

These works have been referred to in such detail as series composed of out patients and patients from private practices are among those that correspond most closely to this work. One cannot escape the fact that these series are more or less selective, consisting of individuals referred for investigation because they were ill or had symptoms or signs of hypertensive disease. There are some further series, among others those of Ehström (58) Masing (140) and Rosling (198) but mainly those follow-up studies dealing with the cardiac manifestations are reported here.

The hospital series are possibly even more selective. Some of these will be considered briefly. Volhard & Fahr's classic account and classification of Bright's

disease has been mentioned earlier (p. 19). One finds here a more exact account of the cardiac manifestations, both the subjective symptoms and the objective findings, but the frequency of the different symptoms and findings is not given in full. In their series composed of 268 cases (149 men and 119 women) of the benign form (*gutartige essentielle hypertonie*) heart failure occurred in 39 of 89 (44 %) individuals who died and in 47 of the 179 survivors (26 %).

Keith, Wagener & Barker (112) were the first to classify hypertension on the basis of the retinal changes. In the more recent classifications proposed by Palmer, Loofbourow & Doering (169) by Smithwick (213) and by Hammarström & Bechgaard (94) the cardiac signs and symptoms together with visceral changes are included in the classification. None of these works state the frequency of the different cardiac signs and symptoms.

In addition there are many well-known works based on hospital series, for instance those of Benni (20) Rasmussen & Boe (187) Griep, Barry Hall & Hoobler (85) and of Marshall (159) and Engel (60). All these authors indicate the importance of the cardiac findings, and in particular emphasise the size of the heart, judged clinically, electrocardiographically and radiologically as a decisive factor in prognosis. No information of the frequency of the different cardiac symptoms and signs is given in these works either.

## Conclusion

An attempt has been made to review some of the literature on cardiac signs and symptoms. (The review does not pretend to be complete, as the literature on this subject is very extensive.)

A critical appraisal shows that there are certain limitations in the works to which reference is made. The main criticism of these series is that they are selected groups, as they are composed of sick people, either in hospital or attending as out-patients, or

the patients of doctors with private practices. Furthermore, in some there is considerable selection as regards sex. The series have also been chosen according to definite classifications of the blood pressure, most often with a fixed borderline regardless of age. Nearly all the studies lack adequate control groups.

None of the works referred to take age distribution into consideration in analysing the frequency of the different cardiac signs and symptoms. Finally one finds that in several studies the frequency calculations have been made with both sexes taken together without analysing each sex separately.

### Formulation of the problem

This review of the literature indicates that there is some connection between the level of the blood pressure and the cardiac signs

and symptoms. But the information is ambiguous. Some of the prognostic studies, for instance that of Blood & Perera, show no definite relationship between the level of the blood pressure and the symptoms and the later development of cardiovascular complications. Other investigations, both follow up studies, experimental, and pathologico-anatomical investigations, however show that there is a certain proportional relationship between the blood pressure and the cardiac signs and symptoms.

It is therefore natural to formulate the following problem

*Is there any relationship in this series between the level of the blood pressure and the different cardiac signs and symptoms?*

How real are these relationships, and can any rules be found from this grouped series?

## Dyspnoea

### Definition

Dyspnoea implies the subjective feeling of difficulty in breathing, in contrast to hyperpnoea or polypnoea which are not accompanied by the subjective feeling of difficulty in breathing. Meakins (146) defines the symptom as consciousness of the necessity for increased respiratory effort.

Cardiac dyspnoea is mainly due to pulmonary congestion which leads to diminution in the respiratory reserve. Dyspnoea on exertion is usually the first sign of a reduced cardiac reserve. To begin with dyspnoea occurs only on great exertion, later on even the slightest effort. When pulmonary congestion becomes marked, dyspnoea is also manifest at rest, particularly on lying flat.

In this series dyspnoea on exertion has been graded as *slight* or *marked dyspnoea*. By marked dyspnoea is meant dyspnoea on exertion that is so evident that the person concerned must stop on hills or going upstairs. A more definite classification, as

proposed by Fletcher (71) has not been found of practical use in this survey because very few individuals complained of severe grades.

An analysis of the relationship between age, blood pressure, and dyspnoea can only be undertaken after all the causes in which causes other than hypertension and hypertensive diseases can explain the symptom have been excluded. Consequently all the cases have been excluded in which the investigation revealed that the heart disease was of a rheumatic, congenital, or luetic nature, together with cases with lung disease, kyphoscoliosis, and cor pulmonale, and also anaemia (see Table 71 subgroup 1).

The series is next depleted of all the cases with kidney disease and other secondary causes of hypertension. The remainder of the series thus consists of the individuals with essential hypertension and of the individuals with a normal blood pressure (Table 71 subgroup 2,

Table 7.1 Distribution of individuals observed in the different subgroups according to sex and age

|                |  | 15-29 |    | 30-39 |     | 40-49 |     | 50-59 |     | 60-69 |     | ≥ 70 |     | Total |     |
|----------------|--|-------|----|-------|-----|-------|-----|-------|-----|-------|-----|------|-----|-------|-----|
|                |  | M     | F  | M     | F   | M     | F   | M     | F   | M     | F   | M    | F   | M     | F   |
| Total material |  | 149   | 57 | 134   | 122 | 126   | 204 | 108   | 196 | 109   | 159 | 57   | 129 | 683   | 867 |
| Subgroups      | 1 Excluding heart and/or lung diseases                   | 143   | 52 | 128   | 114 | 121   | 193 | 102   | 189 | 101   | 156 | 57   | 125 | 632   | 831 |
|                | 2 Excluding secondary hypertension and/or renal diseases | 142   | 48 | 120   | 103 | 120   | 183 | 100   | 180 | 96    | 148 | 55   | 117 | 633   | 779 |
|                | 3 Excluding the overweight                               | 136   | 47 | 114   | 98  | 99    | 171 | 77    | 147 | 76    | 122 | 46   | 103 | 48    | 697 |

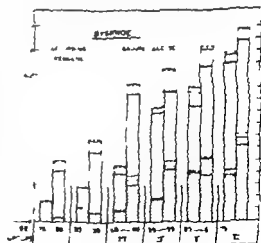
shown in the following Figures by broken lines) The difference in the frequency of the symptom in these two series appears to be minimal (compare Figs. 7.2 and 7.4)

Evaluation of the symptom dyspnoea cannot be entirely correct unless all those who are overweight are also excluded (Table 7.1 subgroup 3)

The individuals in this series are classified as overweight when their weight exceeds the limits for normal weight given by Bøe, Hummerfelt & Wedervang (34) in their Table 47a, page 140, where the calculations are based on the Davenport index.

more commonly than men. The difference is particularly great in the younger age groups and decreases with increasing age.

Fig 7.1 Frequency distribution of dyspnoea in per cent according to age and sex. Hatched rectangles denote marked dyspnoea. The Figure illustrates the small difference between arterial hypertension (—) and essential hypertension (—) On the other hand, the frequency of the symptom is considerably reduced in certain age groups when those who are overweight are excluded (—) The series is divided into sex age groups. In the following Figures these age groups will be designated by the numbers 1-6.



## The influence of age and blood pressure

When the series consisting of the individuals with essential hypertension is divided according to age and sex, regardless of blood pressure, it is found that the symptom shows increasing frequency with increasing age in both sexes. The increase with age is almost linear in both sexes (a linear increase here implies an even increase with age and not a precise numerical relationship)

The Figure shows a distinct sex difference the women have dyspnoea much

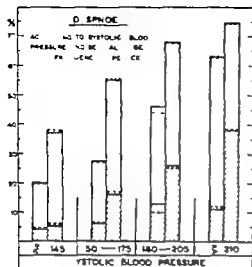


Fig. 7.2. The frequency of dyspnoea in percent according to systolic blood pressure and sex. Hatched rectangles denote marked dyspnoea.

For explanation see Fig. 7.1

Arterial hypertension ———

Essential ———

This sex difference is seen in both slight and marked dyspnoea (hatched rectangles).

When overweight is excluded from the series, the frequency of the symptom decreases (In Fig 7.1 this reduced series is indicated by heavy continuous lines). The greatest reduction is to be seen in women in the 50-59 and 60-69 age groups, while the influence is less marked in men and least in the younger age groups. In the youngest age group the reduction amounts to 1.5 % for men and 6 % for women, while the reduction in the 60-69 age group is 8 % and 9 % respectively. In the whole series the frequency is reduced by 6 % in men and 7 % in women.

On dividing the series into blood pressure groups regardless of age the frequency can be seen to increase with rising blood pressure.

In Fig 7.2 the series is shown classified by the systolic pressure. Here the difference is illustrated between the reduced series,

comprising arterial hypertension (light continuous lines) and the series comprising essential hypertension (broken lines).

The difference in the frequency of dyspnoea in these two groups is minimal. A classification by diastolic pressure of the series gives the same result.

The increase in the frequency of dyspnoea with increasing blood pressure is almost linear in both sexes.

In Fig 7.3 the frequency of dyspnoea is illustrated with the series classified according to the diastolic blood pressure, regardless of age.

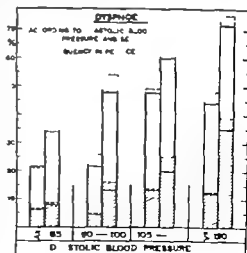
Here the series comprising essential hypertension (broken lines) is compared with the series obtained when overweight patients are excluded (heavy continuous lines). The Figure illustrates the influence of the overweight which appears to be less marked in men. The greatest difference is seen in women in the blood pressure groups 90-100 and 105-115 mm Hg. Similar findings are to be seen on classifi-

Fig 7.3 The frequency of dyspnoea in percent according to diastolic blood pressure and sex. Hatched rectangles denote marked dyspnoea.

For explanation see Fig 7.1

Essential hypertension ———

Excluding overweight ———



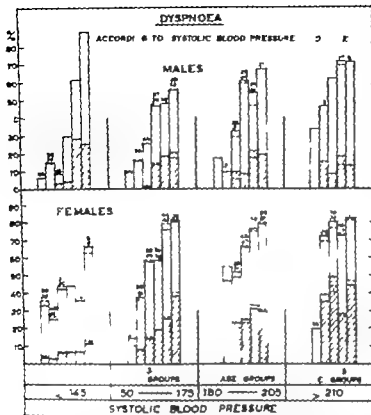


Fig. 74 The frequency of dyspnoea according to blood pressure and age. Hatched rectangles denote marked dyspnoea. Age groups as indicated in Fig. 71 Arterial hypertension (upper figures over the columns) Essential hypertension (sloping figures over the columns).

cation by systolic pressure also, in that the effect of overweight is greatest in women in the two middle blood pressure groups.

Dividing the series in this way however does not give an accurate picture of the influence of age and of blood pressure. The series must be divided into both age and blood pressure groups.

This has been done for both sexes in Fig. 4. The series is divided into 4 blood pressure groups, and each of the blood pressure groups is divided into 6 age groups. In this way the influence of age and that of blood pressure can be studied.

The series is classified by systolic pressure in Figure 74 which illustrates the symptom frequency in this series consisting of arterial hypertension (light continuous lines) and the series comprising essential hypertension (broken lines). Overweight has not been excluded from this series.

The Figure shows the minimal difference between the two groups moreover the marked influence of age is illustrated, as the frequency of dyspnoea increases considerably with increasing age. This age effect is relatively linear.

The sex difference is also seen, and is most marked in the two youngest age groups.

When the series is classified by diastolic pressure similar relationships are apparent (Fig. 75).

In this Figure the series comprising essential hypertension (broken lines) and the series with the overweight excluded (heavy continuous lines) are presented. The Figure shows that the influence of overweight makes itself felt more in women and seems to be most marked in those over 50 years. There does not seem to be any consistent difference between the groups with low or with high blood pressure.

Table 7.2. *Essential hypertension. Frequency of dyspnoea*

Number of individuals with dyspnoea (+) compared to number of individuals in the different age and blood pressure groups (No.)

| Diastolic BP |     | Age groups |       |       |       |       |      | Total |          |
|--------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|              |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| F m a l e    |     |            |       |       |       |       |      |       |          |
| ≤ 85         | +   | 3          | 6     | 8     | 10    | 5     | 6    | 38    | 37       |
|              | No. | 15         | 30    | 19    | 19    | 11    | 10   | 102   |          |
| 90-100       | +   | 9          | 20    | 32    | 43    | 49    | 44   | 217   | 55       |
|              | No. | 34         | 55    | 95    | 86    | 71    | 57   | 396   |          |
| 105-115      | +   |            | 7     | 25    | 31    | 32    | 24   | 119   | 70       |
|              | No. | 1          | 16    | 44    | 40    | 40    | 30   | 171   |          |
| ≥ 120        | +   |            | 2     | 17    | 27    | 20    | 18   | 84    | 76       |
|              | No. |            | 4     | 25    | 35    | 26    | 20   | 110   |          |
| Total        | +   | 12         | 35    | 102   | 111   | 106   | 92   | 458   | 59       |
|              | No. | 48         | 103   | 183   | 180   | 148   | 117  | 779   |          |
| M e n        |     |            |       |       |       |       |      |       |          |
| ≤ 85         | +   | 3          | 3     | 1     | 4     | 10    | 7    | 28    | 21       |
|              | No. | 48         | 53    | 18    | 15    | 12    | 10   | 134   |          |
| 90-100       | +   | 6          | 13    | 11    | 21    | 22    | 16   | 89    | 26       |
|              | No. | 88         | 76    | 64    | 46    | 50    | 21   | 345   |          |
| 105-115      | +   | 2          | 1     | 8     | 14    | 12    | 13   | 50    | 49       |
|              | No. | 6          | 8     | 22    | 23    | 23    | 21   | 103   |          |
| ≥ 120        | +   |            |       | 7     | 8     | 7     | 2    | 24    | 47       |
|              | No. |            | 3     | 18    | 16    | 11    | 3    | 51    |          |
| Total        | +   | 11         | 17    | 27    | 47    | 51    | 38   | 191   | 30       |
|              | No. | 142        | 120   | 120   | 100   | 96    | 55   | 633   |          |

The question is whether the blood pressure has any real influence on the symptom dyspnoea.

When comparing each of the age groups given in Figures 7.4 and 7.5 and Table 7.2 there seems to be a slight increase of the frequency of both grades of dyspnoea with increasing blood pressure in women. This is seen in nearly all age-groups. This tendency is more prominent by the diastolic pressure classification (Fig. 7.5). In men, on the other hand, this tendency is not clearly seen. The blood pressure seems to be of some

influence around the forty and fifty-year age group when all cases of dyspnoea are concerned. In the younger and older age groups the findings are irregular. Marked dyspnoea is not influenced at all by increase in blood pressure. The data, however, are so scanty that it is hardly justifiable to give any calculations.

#### Statistical analysis

A statistical analysis has been made of the series after excluding secondary hypertension and/or renal diseases, classified by

Table 7.3. Essential hypertension. Frequency of dyspnoea

Number of individuals with marked dyspnoea (++) compared to number of individuals in the different age and blood pressure groups (No.)

| Diastolic BP |           | Age groups |       |       |       |       |      | Total |          |
|--------------|-----------|------------|-------|-------|-------|-------|------|-------|----------|
|              |           | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Females      |           |            |       |       |       |       |      |       |          |
| ≤ 85         | ++<br>No. | 13         | 1     | 1     | 3     | 1     | 3    | 3     | 3        |
| 90-100       | ++<br>No. | 1          | 2     | 12    | 16    | 16    | 19   | 66    | 17       |
| 105-115      | ++<br>No. | 1          | 1     | 10    | 9     | 14    | 9    | 43    | 25       |
| ≥ 120        | ++<br>No. |            | 4     | 9     | 14    | 9     | 11   | 43    | 39       |
| Total        | ++<br>No. | 1          | 4     | 32    | 42    | 40    | 42   | 161   | 21       |
| Males        |           |            |       |       |       |       |      |       |          |
| ≤ 85         | ++<br>No. | 48         | 33    | 16    | 15    | 5     | 3    | 8     | 6        |
| 90-100       | ++<br>No. | 88         | 76    | 2     | 5     | 5     | 4    | 16    | 5        |
| 105-115      | ++<br>No. | 6          | 8     | 22    | 3     | 3     | 3    | 12    | 12       |
| ≥ 120        | ++<br>No. |            | 3     | 3     | 1     | 2     |      | 6     | 12       |
| Total        | ++<br>No. | 144        | 120   | 5     | 9     | 18    | 10   | 4     | 7        |

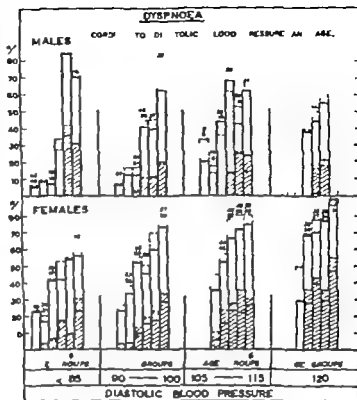
diastolic pressure see Fig. 7.5) The series is grouped in Table 7.2, including all cases of dyspnoea and in Table 7.3 including marked dyspnoea.

According to the principles specified in chapter 4 (p. 47) the statistical analysis of this symptom (both grades combined) has been based on the reduced series. The youngest age group (15-29) has been excluded in both sexes and the age groups 30-39 and 40-49 are combined giving 4 age groups and 4 blood pressure groups.

The analysis of marked dyspnoea is based on 3 blood pressure groups (≥ 100, 105-115 and ≥ 120) keeping the same age groups as mentioned above. In men the figures are low therefore only 2 blood pressure groups (≤ 100 and ≥ 105) and 2 age groups (40-59 and 60 or higher) have been used for the test.

The results derived from the Table show that there is a significant difference in the frequency of both grades combined and of marked dyspnoea between both the age

Fig 7.5. The frequency of dyspnoea according to diastolic blood pressure and age. Hatched rectangles denote marked dyspnoea. Age groups as indicated in Fig. 7.1 Essential hypertension — (upper figures over the columns) excluding the overweight — (lower figures over the columns)



and blood pressure groups in women. In men, however, there is only a significant difference between the age groups.

### The influence of overweight

The diagrams in the Figures 7.1, 7.2 and 7.5 show a drop in the frequency of dyspnoea when the overweight patients are excluded from the series. A closer analysis of the reduced series made up of essential hypertension (Table 7.1 subgroup 2) shows that the over-all frequency of dyspnoea is 30% in men. On excluding the overweight patients from the series the frequency of dyspnoea drops to 27%. The corresponding figures for women are 59% and 54% (see Table 7.5).

To throw more light on this the series has been divided into two blood pressure

groups (Table 7.6). To prevent the groups from becoming too small, blood pressure groups 105-115 and  $\geq 120$  mm Hg measured sitting have been put together into one group ( $\geq 105$  mm). This group will subsequently be referred to as the *high* blood pressure group. Then the blood pressure groups  $\leq 85$  and 90-100 mm have been put into one ( $\leq 100$  mm) group, referred to as the *low* blood pressure group. Both groups have then been divided into the subgroups 'overweight' and 'normal' weight in accordance with the criteria on page 122.

Table 7.6 shows that the frequency of dyspnoea is higher in both sexes among the overweight. This is seen in both the high and low blood pressure groups.

In women the frequency of dyspnoea in the overweight 'high blood pressure



*Table 74 Frequency of diagnoses*  
 The series excluding secondary hypertension and/or renal disease  
 (Table 71 subgroup 2)

| Women      |                  |                  |                 |                 |                 |
|------------|------------------|------------------|-----------------|-----------------|-----------------|
| Diast. BP  | Age groups       |                  |                 |                 | $\chi^2$ test   |
|            | 30-49            | 50-59            | 60-69           | $\geq 70$       |                 |
| All grades |                  |                  |                 |                 |                 |
| $\leq 85$  | $\frac{14}{49}$  | $\frac{10}{19}$  | $\frac{5}{11}$  | $\frac{6}{10}$  | BP (3) 25.4     |
| 90-100     | $\frac{72}{148}$ | $\frac{43}{86}$  | $\frac{49}{71}$ | $\frac{44}{57}$ |                 |
| 105-115    | $\frac{32}{60}$  | $\frac{31}{40}$  | $\frac{32}{40}$ | $\frac{24}{30}$ | Age (3) 26.4    |
| $\geq 120$ | $\frac{19}{29}$  | $\frac{27}{33}$  | $\frac{20}{26}$ | $\frac{18}{20}$ |                 |
| Masked     |                  |                  |                 |                 |                 |
| $\leq 100$ | $\frac{16}{197}$ | $\frac{19}{105}$ | $\frac{17}{82}$ | $\frac{62}{67}$ | BP (2) 16.0*    |
| 105-115    | $\frac{11}{60}$  | $\frac{9}{40}$   | $\frac{14}{40}$ | $\frac{11}{50}$ |                 |
| $\geq 120$ | $\frac{9}{29}$   | $\frac{14}{33}$  | $\frac{9}{26}$  | $\frac{11}{20}$ | Age (3) : 11.5* |
| Men        |                  |                  |                 |                 |                 |
| Diast. BP  | Age groups       |                  |                 | $\chi^2$ test   |                 |
|            | 30-49            | 50-59            | $\geq 60$       |                 |                 |
| All grades |                  |                  |                 |                 |                 |
| $\leq 85$  | $\frac{4}{49}$   | $\frac{4}{15}$   | $\frac{17}{22}$ | BP (3) 4.9      |                 |
| 90-100     | $\frac{24}{140}$ | $\frac{21}{46}$  | $\frac{38}{71}$ |                 |                 |
| 105-115    | $\frac{9}{30}$   | $\frac{14}{23}$  | $\frac{25}{44}$ | Age (2) 51.8    |                 |
| $\geq 120$ | $\frac{7}{21}$   | $\frac{8}{16}$   | $\frac{9}{14}$  |                 |                 |
| Masked     |                  |                  |                 |                 |                 |
| Diast. BP  | Age groups       |                  | $\chi^2$ test   |                 |                 |
|            | 30-59            | $\geq 60$        |                 |                 |                 |
| $\leq 100$ | $\frac{7}{141}$  | $\frac{17}{93}$  | BP (1) 0.4      |                 |                 |
| 105        | $\frac{7}{79}$   | $\frac{11}{38}$  | Age (1) 9.7     |                 |                 |

The figures in parentheses are the degrees of freedom.

Table 7.5. Frequency of dyspnoea in the overweight group compared to the group with normal weight according to age without regard to blood pressure

The series excluding secondary hypertension and/or renal diseases (Table 7.1 subgroup 2). Number of individuals with dyspnoea (+) compared to number of individuals in the different age and weight groups (No.)

| Sex   | Groups     |     | Age groups |       |       |       |       |      | Total |          |
|-------|------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|       |            |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Men   | Overweight | +   | 1          | 4     | 7     | 12    | 15    | 5    | 44    | 52       |
|       |            | No. | 6          | 6     | 21    | 23    | 20    | 9    | 85    |          |
|       | Normal     | +   | 10         | 13    | 20    | 35    | 36    | 33   | 147   | 27       |
|       |            | No. | 136        | 114   | 99    | 77    | 76    | 46   | 548   |          |
| Women | Overweight | +   | 11         | 17    | 27    | 47    | 51    | 38   | 191   | 30       |
|       |            | No. | 142        | 120   | 120   | 100   | 96    | 55   | 633   |          |
|       | Normal     | +   | 1          | 5     | 11    | 30    | 26    | 14   | 87    | 96       |
|       |            | No. | 1          | 5     | 12    | 33    | 26    | 14   | 91    |          |
|       | Normal     | +   | 11         | 30    | 91    | 81    | 80    | 78   | 571   | 54       |
|       |            | No. | 47         | 98    | 171   | 147   | 122   | 103  | 688   |          |
| Total |            | +   | 12         | 33    | 102   | 111   | 106   | 92   | 458   | 59       |
|       |            | No. | 48         | 103   | 183   | 180   | 148   | 117  | 779   |          |

groups is in all 100 % while it is 68 % in those of normal weight. In the men the corresponding figures are 53 % and 46 %. In the low blood pressure group the frequency of dyspnoea is in all 92 % in the overweight women compared to 46 % in those of normal weight. The corresponding figures for men are 51 % and 21 %

#### Statistical analysis

Analysis according to the principles given on page 48 has been performed from the data in Table 7.7 p. 151

In the high blood pressure group in both sexes the two youngest age groups are excluded and the age groups 40-59 are combined. This gives a 2-way classification with 3 age groups and 2 blood pressure groups. In the 'low' blood pressure group the age groups 15-39 are combined in both sexes. In men the age groups of 60 or over are also combined

In the 'high' blood pressure group the  $\chi^2$  test gives a significant difference between the overweight and the normal weight groups in women, but not in men. In the 'low' blood pressure group, however there is a significant difference between these weight groups in both sexes.

Finally the  $\chi^2$  test has been calculated for the reduced series consisting of the normal weight groups divided into 'high' and 'low' blood pressure groups, see Table 7.7 b.

The calculations show a significant difference between the blood pressure groups in women, but not in men.

#### The influence of lability of blood pressure on symptoms and signs

Up to now this symptom has been described by classifying according to the blood pressure in a sitting position. Even though all the measurements were taken personally and under identical conditions,

*Table 7.6. Frequency of dyspnoea in overweight and normal weight groups. Reduced series*  
 Number of individuals with dyspnoea (+) compared to number of individuals in the different age, weight and blood pressure groups (No.)

| Diastolic BP | Groups     |     | Age groups |       |       |       |       |      | Total |          |
|--------------|------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|              |            |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Women        |            |     |            |       |       |       |       |      |       |          |
| ≥ 105        | Overweight | +   |            |       | 3     | 16    | 14    | 5    | 38    | 100      |
|              |            | No. |            |       | 3     | 16    | 14    | 5    | 38    |          |
|              | Normal     | +   |            | 9     | 39    | 42    | 38    | 37   | 165   | 68       |
|              |            | No. | 1          | 20    | 66    | 59    | 52    | 45   | 243   |          |
|              | Total      | +   |            | 9     | 42    | 58    | 52    | 42   | 203   | 73       |
|              |            | No. | 1          | 20    | 69    | 75    | 66    | 50   | 281   |          |
| ≤ 100        | Overweight | +   | 1          | 5     | 11    | 14    | 12    | 9    | 49    | 92       |
|              |            | No. | 1          | 5     | 9     | 17    | 12    | 9    | 53    |          |
|              | Normal     | +   | 11         | 21    | 52    | 39    | 42    | 41   | 206   | 46       |
|              |            | No. | 46         | 78    | 105   | 88    | 70    | 58   | 445   |          |
|              | Total      | +   | 12         | 26    | 60    | 53    | 54    | 50   | 255   | 51       |
|              |            | No. | 47         | 83    | 114   | 105   | 82    | 67   | 496   |          |
| Men          |            |     |            |       |       |       |       |      |       |          |
| ≥ 105        | Overweight | +   | 1          |       | 2     | 5     | 6     | 5    | 19    | 53       |
|              |            | No. | 1          | 2     | 9     | 11    | 6     | 9    | 36    |          |
|              | Normal     | +   | 1          | 1     | 13    | 17    | 13    | 10   | 55    | 46       |
|              |            | No. | 5          | 9     | 31    | 30    | 28    | 15   | 118   |          |
|              | Total      | +   | 2          | 1     | 15    | 22    | 19    | 15   | 74    | 48       |
|              |            | No. | 6          | 11    | 40    | 39    | 34    | 24   | 154   |          |
| ≤ 100        | Overweight | +   | 5          | 4     | 5     | 7     | 9     |      | 25    | 51       |
|              |            | No. | 5          | 4     | 12    | 14    | 14    |      | 49    |          |
|              | Normal     | +   | 9          | 12    | 7     | 18    | 23    | 23   | 92    | 21       |
|              |            | No. | 131        | 105   | 68    | 47    | 48    | 51   | 430   |          |
|              | Total      | +   | 9          | 16    | 12    | 25    | 32    | 23   | 117   | 24       |
|              |            | No. | 136        | 109   | 80    | 61    | 62    | 51   | 479   |          |

as has been explained in detail on p. 63 serious objections can be raised against the evaluation of a series on the basis of these casual blood pressure readings alone.

Measurements taken during rest are universally considered to be of considerably greater prognostic significance. Here better correlation is found between the

level of the blood pressure and the severity of the signs and symptoms than in casual measurements. In most publications the blood pressure taken during rest refers to measurements taken on in-patients. Perera (173) thus holds that in the casual recording of blood pressure, entirely too much emphasis has been placed on the blood pressure level in a given individual

Table 7.7 Reduced series Overweight and normal weight groups

| BP         | Sex   | Weight     | Age groups       |                 |                 | $\chi^2$ test   |
|------------|-------|------------|------------------|-----------------|-----------------|-----------------|
|            |       |            | 40-59            | 60-69           | $\geq 70$       |                 |
| $\geq 105$ | Women | Overweight | $\frac{19}{19}$  | $\frac{14}{14}$ | $\frac{5}{5}$   | Weight (1) 48.5 |
|            |       | Normal     | $\frac{81}{125}$ | $\frac{38}{52}$ | $\frac{37}{45}$ | Age (2) 6.0*    |
|            | Men   | Overweight | $\frac{7}{18}$   | $\frac{6}{6}$   | $\frac{5}{9}$   | Weight (1) 1.5  |
|            |       | Normal     | $\frac{30}{61}$  | $\frac{13}{28}$ | $\frac{10}{15}$ | Age (2) 13.1    |

| BP         | Sex   | Weight     | Age groups       |                  |                 |                 |                 | $\chi^2$ test     |
|------------|-------|------------|------------------|------------------|-----------------|-----------------|-----------------|-------------------|
|            |       |            | 15-39            | 40-49            | 50-59           | 60-69           | $\geq 70$       |                   |
| $\leq 100$ | Women | Overweight | $\frac{6}{6}$    | $\frac{8}{9}$    | $\frac{14}{17}$ | $\frac{12}{12}$ | $\frac{9}{9}$   | Weight (1) 146.8* |
|            |       | Normal     | $\frac{32}{124}$ | $\frac{52}{105}$ | $\frac{39}{88}$ | $\frac{52}{70}$ | $\frac{41}{58}$ | Age (4) 51.6      |
|            | Men   | Overweight | $\frac{4}{9}$    | $\frac{5}{12}$   | $\frac{7}{14}$  | $\frac{9}{14}$  |                 | Weight (1) 8.4    |
|            |       | Normal     | $\frac{22}{236}$ | $\frac{7}{68}$   | $\frac{18}{47}$ | $\frac{45}{79}$ |                 | Age (3) 14.1      |

Table 7.7 b Reduced series Normal weight groups

| Sex   | BP         | 30-39            | 40-49            | 50-59           | 60-69           | $\geq 70$       | $\chi^2$ test |
|-------|------------|------------------|------------------|-----------------|-----------------|-----------------|---------------|
| Women | $\geq 105$ | $\frac{9}{20}$   | $\frac{39}{66}$  | $\frac{42}{59}$ | $\frac{38}{52}$ | $\frac{37}{45}$ | BP (1) 15.2*  |
|       | $\leq 100$ | $\frac{21}{78}$  | $\frac{52}{105}$ | $\frac{39}{88}$ | $\frac{42}{70}$ | $\frac{41}{58}$ | Age (4) 36.3  |
| Men   | $\geq 105$ | $\frac{1}{9}$    | $\frac{13}{31}$  | $\frac{17}{50}$ | $\frac{13}{28}$ | $\frac{10}{15}$ | BP (2) 2.4    |
|       | $\leq 100$ | $\frac{12}{105}$ | $\frac{7}{68}$   | $\frac{18}{47}$ | $\frac{23}{48}$ | $\frac{23}{31}$ | Age (4) 55.3* |

t cannot be used as a prognostic criterion but statistically the higher diastolic values (particularly under resting conditions) do I think, have some prognostic significance

Similarly Smithwick (214) points out that "in all our studies we have classified patients according to their resting blood pressure levels. There is a perfectly definite

increase in the mortality rate for each ten millimetres of mercury increase in diastolic level.

Even though it is generally accepted that the casual blood pressure is of little importance, there are many works that show that these blood pressure measurements cannot be neglected entirely. Many investigations show that those with transient elevation of the blood pressure show a higher frequency of permanent hypertension than those with normal blood pressure. Thus Hines (98) in a follow-up 10 and 20 years later of a series of 1,522 patients from the Mayo Clinic, noticed that a transient elevation of the systolic and diastolic blood pressure into the upper ranges of normal is prognostic of probable subsequent hypertension (defined as above 160 systolic and 100 diastolic) the higher the original reading of blood pressure the higher the incidence of subsequent hypertension. Elevation of the systolic pressure alone is not indicative of subsequent hypertension. 95 mm marks a critical level of the diastolic pressure as to the possible occurrence of subsequent hypertension. Hines has taken the influence of age into consideration, and concludes that the results of his study hold true regardless of the age of the patient.

The authors Lewy Hillman, Stroud & White (124) in works based on medical records of 22,741 officers of the United States Army have found that transient hypertension increases the probability of later development of sustained hypertension and of retirement or death through cardiovascular renal disease. This series was followed up yearly. By sustained hypertension was meant a reading of over 150 mm of mercury systolic or over 90 diastolic, persisting throughout one examination and not followed in subsequent examinations by lower levels. Transient hypertension was taken to mean a reading below these levels.

Thus these authors doubt that one can without further ado, dismiss the casual blood pressure as completely worthless.

In the present series it was impossible to arrange for the blood pressure to be measured during a long period of bed-rest on the other hand there were no difficulties in allowing each individual to lie and relax in a room on his own and then measuring the blood pressure after 30 minutes rest. This has been described in more detail earlier (page 65).

An analysis of the series based on the resting blood pressure is considered to be of importance. It must, however be emphasized that this 'resting blood pressure' is not identical with the resting blood pressure found after a longer time in bed, on which some of the above-mentioned authors base their calculations.

In the last few years some prognostic studies have been published that go into the problem of the 'labile' and the 'stable' (non-labile) blood pressure. However these studies are based on measurements taken over longer periods of time. Thus Mathusen's series (page 119) was divided into a group with a labile diastolic blood pressure (falling during the recording period to values under 95 mm Hg) and a stable group (values never below 100 mm Hg during the recording period). The measurements were taken on in-patients. The mortality figures showed that the group with labile diastolic blood pressures had a mortality rate of the same order as that of the general population, while the group with stable diastolic blood pressure showed a mortality rate that was 6 times greater for women, and 10 times greater for men, than the general mortality rate.

Perera (175) in a work comprising 50 patients with documented hypertensive vascular disease, divided into two equal groups depending on the presence or absence of blood pressure lability has found a significant difference in the mortality of the two groups. While the labile hypertensive patients died, on an average, at 56 years of age, 23 years after the raised blood pressure was noticed, the non-labile group showed an average age

at death of 44 years, 13 years after hyper-tension was discovered. All patients were selected from a series of previously normotensive patients followed up from the known time of onset of hypertension until death from a cause presumably related to their disease, provided only that there was adequate information concerning resting as well as casual blood pressure values. In this work the blood pressure was regarded as *labile* when resting levels were more than 40/20 mm of mercury below average casual levels, as *non-labile* when resting levels were less than 30/15 mm below average casual levels. Casual values refer to single blood pressure determinations secured in the sitting or standing position under quiet conditions in the office or clinic by a physician well known to the ambulatory patient.

In addition Perera found that coronary artery disease and cerebral vascular accidents developed more frequently in the labile series, while retinopathy and renal damage were encountered more commonly in the non-labile group.

As these prognostic studies show a difference in the mortality and the symptomatology it seems pertinent to put forward the following problem:

*Is there any difference in this series, in the frequency of symptoms and signs when the series is grouped into a labile and a non-labile group according to the fall in the blood pressure after 30 minutes rest?*

The question arises as to which way the grouping should be arranged. Should an arbitrary fixed border line between the non-labile and labile groups be chosen — as was done in the works mentioned above? Or should the known difference in the lability of the blood pressure demonstrated in chapter VI be taken into consideration?

In chapter VI it has been found that the blood pressure measured sitting and then lying after 30 minutes rest shows a fall that is greatest in the younger and greatest in those with raised blood pressure (compare Figs. 6.20 and 6.21). This fall is

regular and systematic, and statistical analysis shows a linear relationship of age, sex, and blood pressure to these differences when the mean values of the groups are used (see p. 106).

As the variability of the blood pressure is different in the different age and blood pressure groups, it is not very logical to use a fixed and common blood pressure level as the border line between the non-labile and labile group. A blood pressure that shows a considerable fall during rest, and is thus considered as labile in the higher age groups, may possibly be considered non labile in the younger.

The most logical plan would be to take into consideration this difference between the age groups in the two sexes when classifying the labile and non-labile groups. It has therefore been decided to group the series according to the regression lines shown in Fig. 6.21 which has been worked out from Tables 6.15 and 6.19. Those individuals who, after 30 minutes rest, showed a fall greater than the theoretical group average (given by the regression lines) are hereafter considered as *labile* and the groups of individuals with blood pressure less than the theoretical group average as *non-labile*.

### The influence of lability of the blood pressure on the symptom dyspnoea

In this grouped series an analysis has been made of the frequency of dyspnoea in relation to the lability of the blood pressure, according to the plan outlined in the previous section.

The series has been analysed on the basis of a diastolic pressure classification. The reduced series has been used, consisting of those with essential hypertension and those with normal blood pressure. Finally all the overweight individuals have been excluded.

The analysis has been done in such a way that both the 'high' and the 'low'

Table 7.8. Frequency of dyspnoea in relation to blood pressure lability

Number of individuals with all grades of dyspnoea (+) and those with marked dyspnoea (++) compared to number of individuals in the different age and blood pressure groups (No.)

| Diastolic BP  |               |     | Age groups |       |       |       |       |      | Total |          |    |
|---------------|---------------|-----|------------|-------|-------|-------|-------|------|-------|----------|----|
|               |               |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |    |
| Females       |               |     |            |       |       |       |       |      |       |          |    |
| Sitting ≥ 105 |               | +   |            | 8     | 39    | 40    | 38    | 36   | 161   | 65       |    |
|               |               | ++  |            | 1     | 16    | 20    | 13    | 16   | 66    |          |    |
|               |               | No. | 2          | 24    | 66    | 59    | 52    | 43   | 248   |          |    |
| Resting       | Non-labile    | +   |            | 2     | 28    | 24    | 19    | 20   | 93    | 85       |    |
|               |               | ++  |            |       | 15    | 11    | 9     | 13   | 48    |          |    |
|               |               | No. | 1          | 11    | 42    | 36    | 26    | 26   | 142   |          |    |
|               | Labile        | +   |            | 6     | 11    | 16    | 19    | 16   | 68    | 64       |    |
|               |               | ++  |            | 1     | 1     | 9     | 4     | 3    | 18    |          |    |
|               |               | No. | 1          | 13    | 24    | 23    | 26    | 19   | 106   |          |    |
|               | Males         |     |            |       |       |       |       |      |       |          |    |
|               | Sitting ≥ 105 |     | +          | 1     | 1     | 13    | 17    | 13   | 10    | 55       | 47 |
| ++            |               |     |            |       | 3     | 2     | 7     | 3    | 15    |          |    |
| No.           |               |     | 5          | 9     | 31    | 30    | 28    | 15   | 118   |          |    |
| Resting       | Non-labile    | +   |            | 1     | 8     | 10    | 8     | 6    | 33    | 59       |    |
|               |               | ++  |            |       | 4     | 1     | 4     | 3    | 16    |          |    |
|               |               | No. | 2          | 4     | 14    | 15    | 15    | 6    | 56    |          |    |
|               | Labile        | +   | 1          |       | 5     | 7     | 5     | 4    | 22    | 55       |    |
|               |               | ++  |            |       | 1     | 1     | 3     |      | 5     |          |    |
|               |               | No. | 3          | 5     | 17    | 15    | 13    | 9    | 62    |          |    |

blood pressure groups (see page 127) have been divided into a labile and a non-labile group, according to the drop in the blood pressure after 30 minutes rest lying down. The analysis was made first on the series comprising all grades of dyspnoea subsequently for the individuals showing marked dyspnoea.

#### 1 The high blood pressure group

Table 7.8 shows the frequency of dyspnoea within the different age groups divided into labile and non-labile groups.

In men in all age groups the frequency of all grades of dyspnoea is greater in the non-labile group than the labile group. Thus dyspnoea occurs in all in 59% of the non-labile and in 35% of the labile group. In women however there is

hardly any difference between the labile and the non-labile blood pressure groups. The frequency of marked dyspnoea is slightly greater in the non-labile group in men (in all 18%) than in the labile group (in all 11%). The series, however is made up of a small number of individuals, as only 10 of the 56 individuals in the non-labile group and 5 of the 62 in the labile group showed marked dyspnoea.

In women there is a marked difference between the non-labile (in all 34%) and the labile group (in all 17%).

The findings are illustrated in Figure 7.6.

#### Statistical analysis

In testing all grades of dyspnoea the youngest age group has been excluded in both sexes, thus giving 4 age groups.

Marked dyspnoea occurs so infrequently in men that an analysis of the data would be worthless. In women only 2 age groups have been used (40-59 and 60 or higher)

The results of the  $\chi^2$  test are seen in Table 7.8b, p. 136

Thus there is a significant difference between the labile and non-labile blood pressure group in men with dyspnoea (all grades) and in women when the symptom is graded into marked dyspnoea.

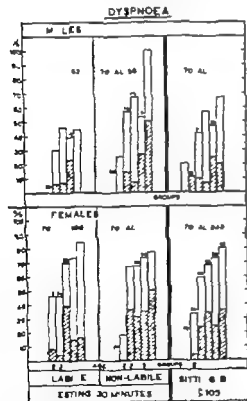


Fig 7.6. The high blood pressure group (sitting BP  $\leq 105$  mm Hg diastolic) divided into labile and non-labile (stable) group according to the drop in the blood pressure after 30 minutes rest lying down. The figure shows greater frequency of dyspnoea within the different age groups in the non-labile group than in the labile group. Hatches rectangles denote marked dyspnoea. Age groups as indicated in Figure 7.1

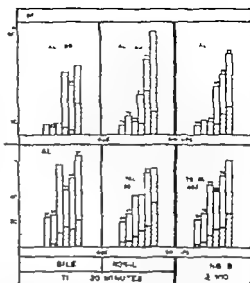


Fig 7.7. When the 'low blood pressure group (sitting BP  $\leq 100$  mm Hg diastolic) has been divided into labile and non-labile group, there is no or only minimal difference in the frequency of dyspnoea within the corresponding age groups in the labile and non-labile groups. For explanation see Fig. 7.6.

## 2. The low blood pressure group.

When the low blood pressure group has been divided into a labile and a non-labile group there is no or only a minimal difference in the frequency of dyspnoea between these groups in both sexes. This applies both when all the individuals with dyspnoea are included and when the individuals with marked dyspnoea are considered.

Thus dyspnoea occurs in men in 21 % in all, in both groups, while marked dyspnoea occurs in 5 % of the non-labile and 4 % of the labile group. In women the total frequency is 41 % in the non-labile and 30 % in the labile while the total frequency of marked dyspnoea is 12 % in both these groups, see Figure 7.7 (The Tables are omitted.)

## Discussion

The symptom dyspnoea is of a subjective character and it is almost impossible to as-



Table 7.8 b All grades of dyspnoea

| Sex   | BP         | 30-49           | 50-59           | 60-69           | ≥ 70            | $\chi^2$ test   |
|-------|------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Women | non-labile | 30              | 24              | 19              | 20              | BP (1) 0        |
|       |            | $\frac{30}{55}$ | $\frac{24}{56}$ | $\frac{19}{26}$ | $\frac{20}{26}$ |                 |
|       | labile     | 17              | 16              | 19              | 16              | Age (3) : 15.0* |
|       |            | $\frac{17}{37}$ | $\frac{16}{45}$ | $\frac{19}{26}$ | $\frac{16}{19}$ |                 |
| Men   | non-labile | 9               | 10              | 8               | 6               | BP (1) 12.0*    |
|       |            | $\frac{9}{18}$  | $\frac{10}{13}$ | $\frac{8}{13}$  | $\frac{6}{6}$   |                 |
|       | labile     | 5               | 7               | 5               | 4               | Age (3) 11.1    |
|       |            | $\frac{5}{22}$  | $\frac{7}{13}$  | $\frac{5}{13}$  | $\frac{4}{9}$   |                 |

Marked dyspnoea

| Sex   | BP         | 40-59           | ≥ 60            | $\chi^2$ test |
|-------|------------|-----------------|-----------------|---------------|
| Women | non-labile | 26              | 22              | BP (1) 10.7   |
|       |            | $\frac{26}{78}$ | $\frac{22}{32}$ |               |
|       | labile     | 10              | 7               | Age (1) : 0   |
|       |            | $\frac{10}{47}$ | $\frac{7}{43}$  |               |

sets accurately in a mass survey of this kind. The evaluation of the symptom is dependent upon the skill and judgement of the observer and in the same way the patient's own power of observation and communicativeness play a great part. To avoid some of these difficulties the symptom has only been graded into three groups: none, slight, or marked; regard less of its duration. In spite of this rather rough grading it is not possible to avoid some variation in the assessment. (This observer error and observer variation will be discussed in general on page 221.) The grading of the symptom differs from that proposed by Fletcher (71) who has proposed 5 clinical grades of breathlessness. A comparison shows that slight dyspnoea is equivalent to grade 1 and marked dyspnoea is fairly equivalent to grade 2. Marked dyspnoea seems in this study more discriminatory as regards sex and age and to some extent as regards blood pressure than slight dyspnoea.

The analyses indicate that sex, age, and to some extent the blood pressure influence the frequency of the symptom. Furthermore, overweight plays a certain part.

The increase in the frequency of dyspnoea with increasing age is clearly seen in all diagrams and is supported by the statistical analysis, and is also seen when the symptom is graded. This increase seems natural and may be the result of decreased function of the circulatory system including that of the lungs. In this investigation the symptom has only been studied subjectively and no tests have been done to differentiate between the pulmonary and cardiac components. According to Norris *et al* (164) the vital capacity decreases nearly 40% between the ages of 20-29 to 70-79. Similar age trends are also demonstrated by Andersen (8). Therefore it is reasonable to suppose that much of this age effect must be due to diminished pulmonary function.

The diagrams show that the symptom frequency increases comparatively evenly with age. Thus it is seen whether the series is classified according to systolic or diastolic blood pressure but the statistical method used gives no indication of the character of this age effect. Further analysis is necessary to find out to what extent this effect is linear.

The sex difference is marked. All the above figures and calculations of the frequency of the symptom show a considerably higher frequency in women. The difference between the two sexes is to some extent dependent upon the age. Below the age of 60 the difference is somewhat greater than in the two highest age groups. Even when those who are overweight are excluded from the series the sex difference is marked. Marked dyspnoea occurs twice as commonly in women in the high blood pressure group ( $\geq 105$  mm Hg diastolic) and this is also true when the series is divided into labile and non-labile groups. In the low blood pressure group ( $\leq 100$  mm Hg diastolic) the symptom occurs almost three times as frequently in women. The simplest explanation of this great difference between the frequencies is perhaps that women notice and complain of their symptoms more. The difference seems to be too large to be explained only as observer variation and differences in attendance rates.

The influence of blood pressure upon the symptom is somewhat less definite, as it is not marked to the same extent in all age groups. There is a greater difference between the higher and lower blood pressure groups in the younger age groups, while in the oldest age groups the frequency is nearly the same. In both sexes the difference seems to be greatest in the 40-49 age group. The statistical analysis takes all these variable factors into consideration.

Figure 7 indicates that there is a difference in the frequency of dyspnoea between groups with labile and non-labile blood pressure in the high blood pressure group. The statistical analyses show

a significant difference in men when all the individuals with dyspnoea are included in the calculations. In women there is also a significant difference between the labile and the non-labile group with marked dyspnoea. On the other hand there is no definite difference between these groups when all the individuals with dyspnoea are included in the calculations. The cause of this difference in the two sexes may partly be explained by slight dyspnoea being relatively more frequent in women than marked dyspnoea in the labile group. Thus this accounts for some of the differences between the sexes in complaining of dyspnoea.

However the varying findings call for care in interpretation. On the whole one must beware of drawing too definite conclusions from investigations which are based on subjective symptoms — even though the examination has been made under the most uniform conditions possible.

The influence of overweight is also clearly seen from the diagrams in Fig 7 1, 7.3 and 7.5 and in Tables 7.6 and 7.7. The statistical analyses show that there is a significant difference between the overweight individuals and those of normal weight.

The reduction in the frequency of the symptoms when the overweight individuals are excluded from the series is greater in women. The influence of overweight makes itself felt more in the 50-59 and 60-69 year groups. This is natural, as overweight is most pronounced in these age groups, particularly in women (see Bøe, Humerfelt & Wedervang, page 123). There is no particular difference between the groups with high and with low blood pressure.

It must be stressed that the norms for normal weight used in this series follow the data given by Bøe, Humerfelt, & Wedervang (34) which are based on the Daven-

port index with  $\frac{W}{H^2} = 22$  for the normal values, given for different heights in both

sexes. These norms show considerable variation as the normal weight for men with a height of 1.0 m shows a range of from 52.7 kg to 79.1 kg the corresponding figures for women of the same height being 48.3 to 83.5. If norms with narrower limits for normal weight had been used, for example the Metropolitan Life Insurance Co. Ideal Weight (147-148) or the norms for normal weight given by Lindberg and co-workers (130) based on the mean value  $\pm 10$  the frequency of the symptom dyspnoea would probably be reduced even further when the individuals who are overweight are excluded from the series.

It is to be expected that most cardiovascular symptoms occur with increasing frequency with increasing age. It is therefore necessary to divide the series according to age. It is very rare, however, to find this in other works on hypertension. Most authors give the frequency of dyspnoea as a percentage of all the cases. In Mathisen's series (144) the prevalence of dyspnoea was 41% in all. Bechgaard (17) gives 40-36% in men and 41% in women at the time of the first investigation. Janeway (105) found dyspnoea in 50% of those who died in the control period and in 38% of those who survived. These data apparently agree well, but the comparisons are not of particular value since the age distribution and the character of the series have not been taken into consideration.

## Summary

Dyspnoea on exertion has been graded as slight or marked. By marked dyspnoea is meant dyspnoea on exertion that is so evident that the person concerned must stop on hills or going upstairs.

The symptom is analysed in relation to sex, age, height, lability of the blood pressure and overweight.

Both grades of dyspnoea show increasing frequency in relation to age in both sexes. This increase is almost linear. The influence of blood pressure is not quite consistent in the two sexes. There is a greater difference between the higher and lower blood pressures in the younger age groups.

Statistical analysis shows a significant difference in the frequency of both grades combined and of marked dyspnoea alone between the age and blood pressure groups in women. In men there is a significant difference only between the age groups.

There is also a significant difference in the frequency of dyspnoea between the overweight and the normal weight groups both in the high (diastolic BP  $\geq 105$  mm Hg) and low (diastolic  $\leq 100$  mm Hg) blood pressure groups in women. In men this difference between the weight groups is only seen in the low blood pressure group.

In the high blood pressure group a significant difference is found between the labile and non labile (stable) groups in men with all grades of dyspnoea, and in women with marked dyspnoea.

## Coronary heart disease

### Definition

In this chapter the coronary diseases are discussed from the point of view of the clinical manifestations: angina pectoris and myocardial infarction.

According to Friedberg (76) the syndrome of *angina pectoris* is based on the following essential features

1. Paroxysmal attacks of pain or discomfort.

2. Short duration
3. Characteristic localization, radiation, and quality
4. Elicited mostly by exertion.
5. Relieved by nitrates or rest.

These criteria have been followed in the collection of these data.

The diagnosis of *myocardial infarction* in this series is based on the clinical history, information from the hospital or the private doctor and the electrocardiographic findings. The diagnosis has been accepted

only in the cases where the information from the hospital or doctor who treated the patient verifies the symptoms given in the history. The diagnosis has further been upheld in the cases where the electrocardiographic findings clearly indicate a previous infarction. Uncertain cases with doubtful ECG findings have been omitted.

This group of illnesses will first be discussed as a whole, then finally the material on myocardial infarction will be treated separately.

Table 7.10 : Prevalence of coronary heart disease according to sex, age and diastolic blood pressure  
Total series

| Diastolic Blood Pressure |        | Age groups |       |       |       |       |      | Total |
|--------------------------|--------|------------|-------|-------|-------|-------|------|-------|
|                          |        | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 |       |
| F m l                    |        |            |       |       |       |       |      |       |
| ≤ 100                    | c.h.d. | 35         | 94    | 4     | 5     | 7     | 11   | 27    |
|                          | No.    |            |       | 126   | 115   | 88    | 76   | 554   |
|                          | %      |            |       | 3.2   | 4.5   | 8     | 15   | 4.9   |
| ≥ 105                    | c.h.d. | 28         | 2     | 12    | 17    | 8     | 8    | 47    |
|                          | No.    |            | 78    | 81    | 71    | 53    | 313  |       |
|                          | %      |            | 7     | 15.4  | 21    | 11    | 15   | 15    |
| Total                    | c.h.d. | 37         | 2     | 16    | 22    | 15    | 19   | 74    |
|                          | No.    |            | 122   | 204   | 196   | 159   | 129  | 867   |
|                          | %      |            | 1.6   | 8     | 11.2  | 9.5   | 15   | 8.5   |
| M l                      |        |            |       |       |       |       |      |       |
| ≤ 100                    | c.h.d. | 142        | 1     | 5     | 4     | 8     | 5    | 24    |
|                          | No.    |            | 120   | 84    | 68    | 72    | 33   | 519   |
|                          | %      |            | 0.8   | 6     | 6     | 12    | 15   | 4.6   |
| ≥ 105                    | c.h.d. | 7          | 14    | 2     | 10    | 6     | 2    | 20    |
|                          | No.    |            | 42    | 40    | 37    | 24    | 164  |       |
|                          | %      |            | 5     | 25    | 16    | 8     | 12   | 12    |
| Total                    | c.h.d. | 149        | 1     | 7     | 14    | 15    | 7    | 44    |
|                          | No.    |            | 134   | 126   | 108   | 109   | 57   | 683   |
|                          | %      |            | 0.8   | 5.5   | 13    | 14    | 12   | 6.5   |

Individuals in the different age and blood pressure groups (%) compared with number of individuals with symptoms of coronary heart disease (c.h.d.)

**Table 7.11 Coronary heart disease**  
according to sex, age and diastolic blood pressure. Series excluding secondary hypertension and renal disease

| Diastolic BP |               | Age groups |       |       |       |       |      | Total |          |
|--------------|---------------|------------|-------|-------|-------|-------|------|-------|----------|
|              |               | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Females      |               |            |       |       |       |       |      |       |          |
| ≤ 100        | c.h.d.<br>No. | 47         | 83    | 114   | 105   | 82    | 67   | 498   | 44       |
| ≥ 105        | c.h.d.<br>No. | 1          | 1     | 11    | 14    | 5     | 6    | 37    | 13       |
| Total        | c.h.d.<br>No. | 48         | 103   | 144   | 119   | 87    | 73   | 594   | 7.6      |
| Males        |               |            |       |       |       |       |      |       |          |
| ≤ 100        | c.h.d.<br>No. | 136        | 109   | 80    | 61    | 62    | 31   | 479   | 44       |
| ≥ 105        | c.h.d.<br>No. | 6          | 11    | 2     | 10    | 4     | 2    | 35    | 12       |
| Total        | c.h.d.<br>No. | 142        | 120   | 82    | 71    | 66    | 33   | 514   | 6.2      |

Individuals in the different age and blood pressure groups (No.) compared with number of individuals with symptoms of coronary heart disease (c.h.d.)

In the series as a whole coronary disease occurs in 44 out of 683 men or 6.5 % and in 74 out of 867 women or 8.5 % (see Table 7.10). The prevalence of angina pectoris excluding those with myocardial infarction is 5 % in men and 7.3 % in women. When all the cases with secondary hypertension and renal diseases are removed from the series, the frequency of coronary disease becomes 6.2 % in men and 7.6 % for women (see Tables 7.11 and 7.12).

### The influence of age and blood pressure

Grouping of the series according to age shows that the frequency increases with rising age in both sexes. This is illustrated in Fig. 7.8. The frequency increases up

to the 50-59 year group whereafter the frequency is nearly constant in both sexes. There is an insignificant sex difference and it is only in the 50-59 and the 60-69 age groups that the coronary diseases occur more frequently in men. No important deviations from these findings are to be seen when the individuals with myocardial infarction are excluded from the series.

The same Figure also shows the prevalence (broken lines) when those with secondary hypertension and renal disease are excluded from the series. This does not lead to any important difference in the frequency in either sex.

Grouping of the series according to a stratification of the systolic and the diastolic blood pressure is shown in Figure 7.9 which shows an increase in frequency with rising blood pressure. The frequency is greatest in women in the highest blood

Table 7.1. *Coronary heart disease*

according to sex, age and systolic blood pressure. Series excluding secondary hypertension and renal disease

| Systolic BP |            | Age groups |       |       |       |       |      | Total |          |
|-------------|------------|------------|-------|-------|-------|-------|------|-------|----------|
|             |            | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Females     |            |            |       |       |       |       |      |       |          |
| ≤ 175       | c.h.d. No. | 48         | 91    | 119   | 99    | 56    | 28   | 441   | 3.4      |
| ≥ 180       | c.h.d. No. |            | 12    | 11    | 16    | 8     | 9    | 44    | 1.3      |
| Total       | c.h.d. No. | 48         | 103   | 130   | 115   | 64    | 37   | 485   | 7.6      |
| Males       |            |            |       |       |       |       |      |       |          |
| ≤ 175       | c.h.d. No. | 136        | 110   | 86    | 63    | 36    | 26   | 447   | 4.8      |
| ≥ 180       | c.h.d. No. | 6          | 10    | 34    | 37    | 40    | 29   | 156   | 10       |
| Total       | c.h.d. No. | 142        | 120   | 120   | 100   | 76    | 55   | 613   | 6.2      |

Individuals in the different age and blood pressure groups (No.) compared with number of individuals with symptoms of coronary heart disease (c.h.d.)

pressure groups apart from this there is little sex difference. The difference in prevalence between the total material and the series when those with secondary hypertension and renal disease are excluded is seen mainly in the highest blood pressure groups (diastolic  $\geq 120$  and systolic 180-205  $\geq 210$  mm) measured in the sitting position.

If the series is divided into the 4 blood pressure groups mentioned earlier and each of the blood pressure groups again divided into 6 age groups, the relationship between age and blood pressure and the prevalence of the coronary diseases can be studied more closely. As the prevalence of coronary disease is relatively low in order to form large enough groups two blood pressure groups only have been used ( $\leq 100$  and  $\geq 105$  mm diastolic or 175 and  $\geq 180$  systolic). Next these

two groups have been divided into 6 age groups (see Table 7.10).

On considering the first group with *low blood pressure* an increase in frequency with rising age is to be seen in both sexes. This influence of age is illustrated in Fig. 7.10. The increase is quite even in men according to both classifications. In women the increase is rather steep on systolic classification. Apart from this the similarity between both the sexes is striking.

The average prevalence rate of coronary disease in men is 4.6% when the total series is classified by diastolic pressure ( $\leq 100$  mm) and 5% when it is classified by systolic pressure ( $\leq 175$  mm). The corresponding figures for women are 4.9 and 3.7.

In the groups with *high blood pressure* ( $\geq 105$  mm diastolic or  $\geq 180$  mm systolic) the total prevalence is two to three

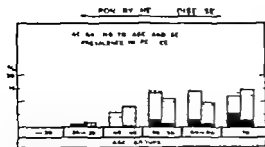


Fig. 7.8. The prevalence of coronary heart disease according to age and sex. Black columns denote myocardial infarction. Total series — Series excluding secondary hypertension and renal disease —

times greater than in the groups with low blood pressure. Thus it is 12% and 11.6% in men and 15% in women according to each classification (see Table 7.10). The frequency in women is greatest in the 40-49 and 50-59 age groups in both classifications, while in men an increase is to be seen mainly in the 50-59 age group. The prevalence in the two highest age groups is, on the other hand, lower than in the 50-59 age group. This can be seen in both sexes, on classification both by systolic and diastolic pressure. Figure 7.10 illustrates this and shows that the frequency diminishes in the highest age groups in both sexes. In men the drop is even. In women the frequency is very slightly greater in the highest age groups in comparison with the 60-69 age group.

### The influence of overweight

The significance of overweight in the cardiovascular diseases has been discussed in numerous mortality morbidity and prognostic studies.

The literature shows that all the surveys from life insurance medicine come to the same conclusion: that the mortality is greater among the overweight. Information from these studies is most abundant on the relation to circulatory disorders, because cardiovascular and renal diseases

cause such a large part of the mortality figures.

Only the more recent contributions will be referred to.

In a larger series composed of 25 998 men and 24,901 women that was followed for 25 years, Armstrong Dublin Wheathly & Marks (9) found that degenerative diseases of the heart, arteries and kidneys were 70% greater than expected among the overweight. In a series consisting of 200 000 insured lives Dublin & Marks (56) found that the mortality rate for those with angina pectoris was 14 and 16 per 100 000 among the under and normal-weight individuals in contrast to 33 per 100 000 among the overweight. Finally the investigation showed increased mortality with rising degrees of overweight. Division of the series into the age groups of over and under 45 years showed the same tendency. In the same way Dublin & Marks (later) investigations (57) point in the same direction. The mortality among 50 899 men and women with higher premiums on account of their excess weight who were followed up for 25 years, was 45% higher in those who

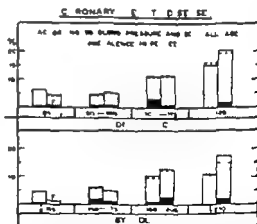


Fig. 7.9. The prevalence of coronary heart disease according to blood pressure and sex. Black columns denote myocardial infarction. Total series — Series excluding secondary hypertension and renal disease —

## CORONARY HEART DISEASE

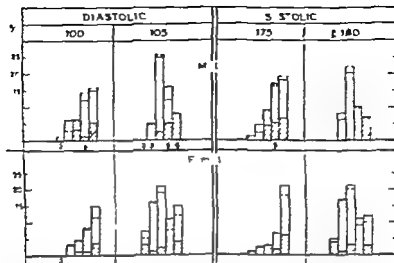


Fig 7-10. The prevalence of coronary heart disease according to age, sex, and blood pressure. Hatched columns denotes myocardial infarction. Total series ———. Series excluding secondary hypertension and renal disease ———.

were moderately overweight and 65 higher in those markedly overweight. The bulk of the mortality was due to cardiovascular and renal disease, primarily of arteriosclerotic origin.

The influence of overweight on the coronary diseases, however, is not uniform.

Moritz & Zamchek (153) found 350 cardiac deaths in an autopsy series made up of 1000 soldiers, aged from 18 to 40 years, who were previously apparently well and in whom collapse and death occurred so quickly that it was not possible to come to any ante mortem diagnosis. An analysis of 115 of these soldiers in whom death was due to coronary disease showed that the weight was significantly higher in this group than in those recorded for healthy inductees — on the other hand there was no difference if the group was compared with soldiers dying from accidental injuries.

Yater and co-workers (24) came to similar conclusions from a series of soldiers,

consisting of 866 individuals under 40 years of age. The diagnosis was reached at necropsy in 450 cases. French and Dock (75) had worked on some of this material previously (80 cases) and concluded that overweight was an important aetiological factor. But this conclusion is due to the weight of the group of fatal cases being compared with weight norms based on the weight of soldiers at the time of induction to the army. When Yater and his co-workers compared a total of 450 fatal cases with a group of soldiers of the same age and length of service who had suffered from military accidents, they found that there was no difference in the weight distribution.

Similarly Levy and co-workers (125) in their prognostic study of 22,741 army officers found that overweight alone did not increase to a significant degree the death rate with cardiovascular-renal diseases. In addition, Garm and his co-workers (77) have investigated the weights



of 97 men who had suffered from myocardial infarction before the age of 40 years and had later become active again. Comparison with 146 healthy men showed that there was no real difference in the relative weights of the two groups.

In addition Keys (113) did not find any difference either in the average weights of a group of 60 consecutive cases of men with definite coronary disease between the ages of 46 and 62 and a group of healthy men of the same age and height.

On the other hand, there are investigations of large population series from the U.S.A. confirming the life insurance studies. Thus the Framingham study by Dawber Moore & Mann (48) showed that among men between 45 and 62 years fatness was associated with the development of coronary heart disease. The study is concerned with measurements of the extent and development of cardiovascular disease in a cross-section of the population aged 30-59 on 1 January 1950, and is planned to continue for 20 years. The investigation covers 4 469 individuals, 2,024 men and 2,445 women, making up 68.6% of the total sample.

The observed incidence rate of cardiovascular disease in men with a Framingham relative weight of 120 or more was about twice that of the entire population and three times that of men with a relative weight of less than 100. However there was little or no relationship between moderate obesity and new arteriosclerotic heart disease. High blood pressure was significantly associated with the incidence of arteriosclerotic heart disease and there was an increased risk with elevated cholesterol levels. Combinations of these three factors produced groups of men from 45 to 62 years with still higher risks of developing arteriosclerotic heart disease.

The Albany investigation, by Doyle, Healin, Hilleboe, Formel & Kornus (54) covers 1,913 male New York State civil service employees (89% of those eligible) aged from 39 to 55 years, investigated between February 1953 and September

1954. A body weight up to 59% over the Metropolitan Life Insurance Company standard weight carried little increased risk of coronary heart disease while gross overweight, defined as a level 40% or more over ideal weight quadrupled the risk. Increase of body weight of more than 20% above any weight level existing at the age of 25 doubled the risk of developing coronary heart disease.

The Los Angeles investigation by Chapman Goerke Dixon Loveland & Phillips (39) is based on a sample of city civil service employees in Los Angeles in 1949. A total of 2,252 persons, 1,859 men and 393 women aged from 18 to 70 years were investigated. 25% refused to participate or were not available. The incidence of new cases of coronary heart disease among males of 40 to 54 years of age was highest in the heavy height-weight index class (5.2%) and lowest in the light class (0.9%). But in the 55 to 70 year group the incidence among males in the light classes was similar to the incidence in the heavy classes.

No analyses of the significance of overweight are to be found in the works on hypertension referred to previously on page 117.

The findings quoted are thus somewhat contradictory. In the mortality studies from the life insurance companies, in which the weight norms are based on the weight records at the time the policy was issued or in the studies based on the weight of soldiers on enlistment it can be seen that overweight has a considerable influence on the cardiovascular diseases. In the mortality studies in which the weight is compared with that of representative groups of the same sex and age (and length of service in the case of soldiers) no definite influence of overweight is to be found. With the exception of the population series from the U.S.A. there are few clinical studies covering large populations on the influence of overweight on coronary disease. Several of the series are based only on data concerning extreme

degrees of overweight, varying from 20 to 75% overweight. There is hardly any doubt that such extremely overweight people would show increased morbidity and mortality but it is doubtful whether there is any relationship between the lesser degrees of overweight and increased morbidity and death rates.

Thus there are few convincing series indicating that fatness and overweight are important factors in the coronary diseases. None the less fatness will represent a mechanical load on the cardiovascular system. Therefore it is not entirely unreasonable that overweight should affect the individuals in the long run.

Consequently the following problem has been set up: Has overweight any influence in this grouped series?

#### *Present series*

The analyses have been done in accordance with the methods described for the symptom dyspnoea (p. 127).

The series has been limited to those with essential hypertension and those with normal blood pressure.

Table 7.13 shows the prevalence of coronary disease in the overweight group and in the group of those who are not overweight.

The over-all prevalence in the overweight group is 10.6% in men, and 13.4% in women. In the non-overweight group the corresponding figures are 5.5% and 7.1%.

It was shown earlier that hypertension has an influence on the prevalence of the coronary diseases. To guard against the above figures being due to a summation effect of both high blood pressure and overweight, the series has been divided into groups with high ( $\geq 105$  mm) and low ( $\leq 100$  mm) diastolic blood pressure (see p. 127).

It appears that the findings are not identical in both sexes. Thus grouping of the series in the high blood pressure

*Table 7.13. Coronary heart disease*

according to sex, age and weight. Series excluding secondary hypertension and renal disease

| Weight groups |               | Age groups |          |           |           |           |           | Total     |          |
|---------------|---------------|------------|----------|-----------|-----------|-----------|-----------|-----------|----------|
|               |               | 15-29      | 30-39    | 40-49     | 50-59     | 60-69     | ≥ 70      | No.       | Per cent |
| F m l         |               |            |          |           |           |           |           |           |          |
| Overweight    | c.h.d.<br>No. |            |          | 3<br>12   | 7<br>33   | 1<br>24   | 11<br>18  | 11<br>82  | 13.4     |
| Normal weight | c.h.d.<br>No. | 32<br>103  | 2<br>103 | 11<br>171 | 11<br>147 | 11<br>124 | 15<br>104 | 50<br>701 | 7.1      |
| Total         | c.h.d.<br>No. | 32<br>103  | 2<br>103 | 14<br>183 | 18<br>180 | 12<br>148 | 15<br>117 | 61<br>783 | 7.6      |
| M l           |               |            |          |           |           |           |           |           |          |
| Overweight    | c.h.d.<br>No. | 6<br>6     | 6<br>11  | 1<br>11   | 4<br>3    | 3<br>70   | 1<br>9    | 9<br>85   | 10.6     |
| Normal weight | c.h.d.<br>No. | 136<br>114 | 1<br>114 | 3<br>97   | 10<br>77  | 10<br>76  | 6<br>46   | 30<br>548 | 5.5      |
| Total         | c.h.d.<br>No. | 14<br>140  | 1<br>120 | 4<br>100  | 14<br>100 | 13<br>76  | 7<br>55   | 39<br>633 | 6.1      |

Individuals in the different age and weight groups (No.) compared with number of individuals with symptoms of coronary heart disease (c.h.d.)

Table 7.14 Coronary heart disease

Influence of overweight in different blood pressure groups. Series excluding secondary hypertension and renal disease

| BP     | Weight        |            | Age groups |         |          |          |         |         | Total     | Per cent |
|--------|---------------|------------|------------|---------|----------|----------|---------|---------|-----------|----------|
|        |               |            | 15-29      | 30-39   | 40-49    | 50-59    | 60-69   | ≥ 70    |           |          |
| Female |               |            |            |         |          |          |         |         |           |          |
| ≥ 105  | Over weight   | c.h.d. No. |            |         | 2<br>3   | 5<br>16  | 14      | 5       | 7<br>38   | 18.4     |
|        | Normal weight | c.h.d. No. | 2          | 2<br>70 | 9<br>66  | 9<br>59  | 5<br>51 | 7<br>45 | 32<br>244 | 13.1     |
|        | Total         | c.h.d. No. | 2          | 7<br>20 | 11<br>69 | 14<br>77 | 5<br>66 | 7<br>50 | 39<br>282 | 14       |
| ≤ 100  | Over weight   | c.h.d. No. |            |         | 1<br>9   | 2<br>17  | 1<br>10 |         | 4<br>44   | 9.1      |
|        | Normal weight | c.h.d. No. | 50         | 83      | 2<br>10  | 2<br>88  | 6<br>72 | 8<br>59 | 18<br>457 | 4        |
|        | Total         | c.h.d. No. | 50         | 83      | 3<br>114 | 4<br>105 | 7<br>82 | 8<br>67 | 22<br>501 | 4.4      |
| Male   |               |            |            |         |          |          |         |         |           |          |
| ≥ 105  | Over weight   | c.h.d. No. | 1          | 2       | 9        | 3<br>9   | 6       | 1<br>9  | 4<br>36   | 11       |
|        | Normal weight | c.h.d. No. | 5          | 9       | 2<br>31  | 7<br>30  | 4<br>28 | 1<br>15 | 14<br>118 | 11.8     |
|        | Total         | c.h.d. No. | 6          | 11      | 2<br>40  | 10<br>39 | 4<br>34 | 2<br>24 | 18<br>154 | 11.7     |
| ≤ 100  | Over weight   | c.h.d. No. | 3          | 4       | 1<br>12  | 1<br>14  | 3<br>14 |         | 5<br>49   | 16.2     |
|        | Normal weight | c.h.d. No. | 131        | 105     | 1<br>68  | 3<br>47  | 6<br>48 | 5<br>31 | 16<br>430 | 3.7      |
|        | Total         | c.h.d. No. | 136        | 109     | 2<br>80  | 4<br>61  | 9<br>62 | 5<br>31 | 21<br>479 | 4.4      |

Individuals in the different age and blood pressure groups (No.) compared with number of individuals with symptoms of coronary heart disease (c.h.d.)

group (≥ 105 mm diastolic) shows that the over-all prevalence of coronary disease in men is about as great in the overweight (11%) as in those who are not overweight (11.8%). On the other hand the prevalence in the overweight in the low blood pressure group (≤ 100 mm) is markedly greater than in those who are not over-

weight (10% to 3.7%). In women the prevalence among the overweight is greater than in those who are not overweight in both blood pressure groups. Thus the prevalence rate in the high blood pressure group is 18.4% to 13.1% while in the low blood pressure group the figures are 9.1% to 4.4%.

All the prevalence rates given are over all figures. When the series is grouped, as shown in Tables 7 13 and 7 14 the figures within each cell are so small that the conditions for using the statistical method given on p. 47 are not fulfilled

### The influence of the lability of the blood pressure

As in earlier analyses (dyspnoea p 133) the prevalence of the coronary diseases, in relation to the lability of the blood pressure, has been investigated. All cases of secondary hypertension and renal disease and all those who were overweight have been excluded from the series.

In women the group  $\geq 105$  mm diastolic pressure shows that the frequency of coronary disease is greater in the non-labile group (15.5 %) than in the labile group (10.4 %). This difference is due to the fact that the 40-49 age group showed a frequency of 25 % in the non-labile to 0 % in the labile group. In the remaining age groups the prevalence is about the same in both the groups.

In men, on the contrary the prevalence rate is greater in the labile group (15 %) in comparison with the non labile (9 %).

For the groups  $\leq 100$  mm there is no difference in men between the labile and non-labile groups, as the symptom occurs in 3.7 % in both. In women the difference is insignificant, as coronary disease occurs in 4.4 % of the non-labile group and in 3.1 % of the labile group.

The relatively low prevalence of coronary disease in the two sexes must be expected to give rise to varying data and the findings in this series could undoubtedly be due to chance. The Tables and calculations have been omitted.

### Myocardial Infarction

The prevalence of myocardial infarction was, as expected, low on the whole. In the total series (1,550 people) myocardial infarction occurred in 19 individuals, that

is, 1.2 % of whom 10 were men (1.5 %) and 9 women (1 %). The prevalence was, as expected, somewhat greater in the higher age groups, increasing in men from 2.8 % in the 50-59 year group to 7 % in the over-seventies. In women few cases occurred under 50 years of age, increasing to 3.1 % in the highest age group. This is shown in Fig. 7.8 (black columns).

One individual (63 years) showed secondary hypertension as the result of pyelonephritis, 2 individuals (1 man, 71 years and 1 woman, 58 years) had uncomplicated diabetes. Grouping of the total series according to the blood pressure, regardless of age, shows no increase in frequency with rising blood pressure (see Fig. 7.9).

When the series is stratified into blood pressure and age groups, a slight tendency to an increased frequency is to be seen in the higher blood pressures, when the series is classified by diastolic pressure. The prevalence in men with a diastolic blood pressure of  $\geq 105$  mm Hg is 3 % and in the groups  $\leq 100$  mm Hg 1 %. In women the corresponding figures are 1.6 % and 0.7 %. This is shown in Table 7 15.

When the series is classified by systolic pressure one does not see any increase in men with higher blood pressures. In the group  $\leq 175$  mm the frequency is 1.6 % and in the group  $\geq 180$  mm it is 1.3 %. The women on the contrary show an increase from 0.4 % to 1.8 % in the same groups.

Estimation of the prevalence rate on the basis of the blood pressure alone will be of limited value as the drop in the blood pressure may persist after a myocardial infarction. In the cases in which heart failure is present the drop in the blood pressure will be quite marked. This drop is, in such cases, most pronounced in the systolic pressure. The findings in men could point in this direction. Finally 1 man and 3 women showed manifest symptoms of heart failure. The possibility cannot be excluded therefore that some may have shown a fall in blood pressure.

Table 7.15. Myocardial infarction  
according to sex, age and blood pressure

|           |       |              | Age groups |       |       |       |       |      | Total |          |
|-----------|-------|--------------|------------|-------|-------|-------|-------|------|-------|----------|
|           |       |              | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Female    |       |              |            |       |       |       |       |      |       |          |
| Systolic  | 175   | m. l.<br>No. | 56         | 103   | 129   | 106   | 60    | 13   | 466   | 0.4      |
| BP        | ≥ 180 | m. l.<br>No. | 1          | 19    | 75    | 90    | 98    | 3    | 7     | 1.8      |
| Diastolic | ≤ 100 | m. l.<br>No. | 53         | 91    | 126   | 115   | 88    | 2    | 4     | 0.7      |
| BP        | ≤ 100 | m. l.<br>No. | 2          | 1     | 1     | 1     | 71    | 2    | 53    | 1.6      |
| Total     |       | m. l.<br>No. | 57         | 124   | 204   | 196   | 159   | 4    | 9     | 10       |
| Male      |       |              |            |       |       |       |       |      |       |          |
| Systolic  | 175   | m. l.<br>No. | 141        | 120   | 90    | 68    | 60    | 2    | 8     | 1.6      |
| BP        | ≥ 180 | m. l.<br>No. | 8          | 14    | 36    | 40    | 49    | 2    | 29    | 1.3      |
| Diastolic | ≤ 100 | m. l.<br>No. | 14         | 120   | 81    | 68    | 72    | 33   | 5     | 1.8      |
| BP        | ≥ 103 | m. l.<br>No. | 7          | 14    | 42    | 40    | 37    | 2    | 5     | 3        |
| Total     |       | m. l.<br>No. | 149        | 134   | 126   | 108   | 109   | 4    | 10    | 1.5      |

Number of individual (No.) in the different age and blood pressure groups, compared with number of individuals with myocardial infarction (m. l.)

On ophthalmoscopy no wide divergencies were found between the changes in the optic fundi and the blood pressure, with one exception that of a 65-year-old man with auricular fibrillation and a blood pressure of 160/110 who showed findings typical of Keith and Wagener's grade 3

The incidence of *acromegaly* is low in the cases with infarction. Only 1 man and 2 women could be classified as overweight in

accordance with the criteria laid down on p. 122

The frequency of myocardial infarction in relation to the *lability* of the blood pressure shows that, in women, 8 of 9 individuals can be placed in the non-labile groups, and 4 of these individuals in the non-labile high blood pressure group. In men there are 7 individuals in the non-labile groups of whom only 2 individuals fall into the non-labile high blood pressure group.

The infarct series is so small that this distribution could occur by chance.

One must be particularly careful in the evaluation of this series because of the blood pressure changes that may persist after a myocardial infarction.

## Discussion

There are several surprising facts about the prevalence of coronary disease in this series.

However comparison with other morbidity studies is difficult. Firstly this series shows skewed distributions, as most of the individuals have raised blood pressure owing to the fact that the series was chosen according to different selection percent ages in the different blood pressure strata and age groups. Secondly most studies of the prevalence of the coronary diseases are more or less selective and very few consider the prevalence in relation to the blood pressure.

The *over-all frequency* of coronary disease in this series is 6.5 in men and 8.5 in women (the ratio men: women is 1:1.3). When all the individuals with secondary hypertension and renal disease are excluded the prevalence becomes 6.2 in men and 7.6 in women (1:1.2). When the overweight individuals are also removed from the series, the frequency is reduced to 5.5 in men and 7.1 in women (1:1.3). On considering the cases of angina pectoris separately after excluding the individuals who have had infarcts, the frequency in the total series is reduced to 5.4 in men and 7.3 in women (1:1.4).

These over-all frequency data, however tell us very little as age and blood pressure have been shown to be of considerable influence particularly when the series show skewed distributions.

However it has been found that the prevalence rate is 3 times greater in those with high blood pressure than in those with lower. This is evident when the series is divided into two such groups as are

shown on p. 139. Oddly enough, the influence of age is different when the series is divided into groups with high and low blood pressure, as is seen from Table 7 10 and Fig 7 10.

Comparison with other prevalence studies, therefore, is difficult.

If one first considers the studies based on hypertensive series one finds very varying data. Thus Paullin, Bowcock & Wood (171) give 8.4% for angina pectoris and 1.8% for coronary occlusion, Perera (174) gives 16% for angina pectoris and 8% for myocardial infarction, and Jane way (105) found angina pectoris in 17%. The findings in Ayman & Pratt's (13) and in Ribensan & Weiss's (190) studies are not very precise.

In these hypertensive studies the frequency of coronary disease is unfortunately not given separately for men and women, so that the relationship between the findings in the two sexes cannot be studied. In Mathisen's prognostic study (144) the frequency of coronary disease is not mentioned. The prevalence of angina pectoris in Bechgaard's series (17) was 6.1% in men and 2.9% in women at the time of the first recording. Thus the relationship between men and women was 2:1.

Next, on considering some of the many studies in which the series have been selected on the basis of the diagnosis of coronary disease a marked difference is to be found in the distribution in the two sexes. In this series the prevalence in the total series is somewhat higher in women (1.2:1) while almost all the studies of coronary disease give a considerably higher frequency in men, varying from 3:1 up to 6:1.

In a prognostic study of over 3440 patients with angina pectoris from the Mayo Clinic, Parker, Dry, Willis & Gage (170) found the ratio to be 4.3:1. Similar ratios are to be found in series made up of private patients. Levy & Bias (122) found that the ratio was 4.9:1 in a series, from a large office practice

*Table 7 16. Percentage prevalence of coronary heart disease at initial investigation*  
Males

| Report                          | Number of people | Age groups |       |       |       |      |
|---------------------------------|------------------|------------|-------|-------|-------|------|
|                                 |                  | 30-39      | 40-49 | 50-59 | 60-69 | ≥ 70 |
| 1) Framingham                   | 624              | 0.5        | 0.9   | 6.0   |       |      |
| 2) Albany                       | 1,913            | 1.~        | 2.6   | 7.1   |       |      |
| 3) California a) Phillips & al. | 1,839            | 0.4        | 1.1   | 4.8   | 9.3   |      |
| " b) Longshoremen               | 3,694            | 0.4        | 1.4   | 4.2   | 9.7   |      |
| c) Health Survey                | 7,931            | 0.2        | 0.9   | ~4    | 4.6   |      |
| Own material: Total             | 683              | 0.8        | 5.5   | 13    | 14    | 1    |
|                                 | (479)            | (0.8)      | (~5)  | (6.5) | (14)  | (16) |

Adapted from 1) Dawber *et al* (48) 2) Doyle *et al* (54) and reproduced from Drak *et al* (*Amer J publ. Hlth*, 4 5, 1937)

The present series shows markedly skewed blood pressure distributions. Therefore the figures for the series excluding all individuals with secondary hypertension and all with a diastolic BP  $\geq 105$  mm has been given in parentheses.

nating all the individuals with secondary hypertension renal disease and all with a diastolic blood pressure  $\geq 105$  mm (marked in the Table) one find good agreement with the Albany series. A correction of this kind is only approximately correct it is evident that one would also find many individuals with a diastolic blood pressure of over 105 mm in a sample of the general population.

It is difficult to make a similar Table on the prevalence in women as there is much less information. In comparison to the Framingham investigation the prevalence in women in the present series, excluding all the individuals with secondary hypertension and those with a diastolic blood pressure  $\geq 105$  mm, is considerably higher in the 40-49 year group being 2.6% to 1.~. It is 3.8% compared to 2.3% in the 50-59 year group.

It has been pointed out previously that the difference in frequency between the two sexes is not the same in all the age groups. Block, Crumpacker Dry & Gage (27) found that the sex ratio men/women was 6/1 in the 5th decade compared to 3.5/1 in the 7th and 8th decades. Their series from the Mayo Clinic was made up of a total of 6 882 cases of angina pectoris reinvestigated after 5 and 10 years. Similarly

in a series of 865 patients, suffering from an acute coronary episode Peel (172) found a ratio of 4/1 varying from 7/1 under 50 years of age to almost 10/1 between 50-59 years and under 2/1 over 70 years.

In this series the prevalence of coronary disease is greater in men only in the age groups 50-59 and 60-69 years but the margin is very small (see Table 7 10). In the 50-59 age group the ratio is 1.2/1 and in the 60-69 age group 1.5/1. In the remaining age groups the prevalence is greatest in women. The ratios remain the same when all cases of secondary hypertension renal disease and all cases with cardiac disease from causes other than hypertension and arteriosclerosis are excluded from the series.

On dividing the series into a group with low blood pressure (diastolic  $\leq 100$  mm or systolic  $\leq 175$  mm) and a group with high blood pressure (diastolic  $\geq 105$  mm or systolic  $\geq 180$  mm) there is a change in the sex distribution. In the low blood pressure groups the prevalence is greatest in men in all age groups from 30-69 years and the ratio men/women varies from 1.4 to 1.9/1. In the highest age group the ratio is even (see Table 7 10). On the other hand in the high

blood pressure groups the prevalence is greater in the women except in the above-mentioned 50-59 and 60-69 age groups, on diastolic classification of the series. The greatest sex difference is to be seen in the 40-49 age group on both systolic and diastolic classification as the ratio women men is here 3 : 1.

Thus there is a considerable difference in the sex distribution in this morbidity study in comparison to many other morbidity mortality and pathologico-anatomical studies.

The diagnosis of angina pectoris from chest pains of different aetiology can be difficult and the possibility cannot be excluded that some cases have been incorrectly classified as such, but as the author has all the time been aware of this differential diagnostic point, it is hardly likely that there are many such misdiagnosed cases.

The greater morbidity in women in relation to the low death rate given in the mortality statistics could indicate that the development and course of the coronary diseases are different in the two sexes, the men showing a more severe course with greater mortality.

Several authors have maintained that the influence of hypertension on the development of coronary disease is particularly marked in women. White (233) as well as Eppinger & Levine (61) Levy & Boas (122) and Mackenzie (133) point out this sex difference.

The coronary diseases occur with increasing frequency with increasing age so that, according to Friedberg this group of illnesses is the commonest of the heart diseases after the age of 40 years. This increase in coronary sclerosis and the clinically manifest coronary diseases with increasing age is to be seen both in the autopsy series and in numerous clinical studies.

In 1934 Levy, Bruen & Kurtz (123) published a clinical and pathologico-anatomical investigation based on an autopsy series over the years 1910-31. In

all there were 762 autopsy records showing involvement of the coronary arteries, that is 25.9% of the total of 2,877 autopsies. The analyses showed, among other things, an increase in the coronary diseases with increasing age. Thus over the years 1920-31 coronary disease occurred in 19% of those aged 25-44 years, in 40% of the group 45-64 years and in 60% of those over 65 years. Similar influences of age have been found by Gordon Bland & White (80) and Williams, Smith & Sprague (234).

This age influence appears somewhat differently in the two sexes. White, Edwards & Dry (232) found that in men the degree of sclerosis increased greatly from 30 years of age to a maximum in the 50-59 age group whereafter there was no increase with increasing age. Their investigation covered 600 autopsies (100 individuals in each 10-year class from 30 to 89 years). An investigation on the same number of women, using exactly the same methods of analysis, carried out by Ackerman Dry & Edwards (1) showed that the degree of sclerosis increased evenly and constantly from the 4th to the 8th decade after this there was no noteworthy increase with increasing age.

The present series also shows a considerable age influence in both sexes. However this influence is different when the material is divided to groups with high and low blood pressure.

In the groups with low blood pressure a distinct increase is to be seen in the frequency of coronary disease with increasing age in both sexes. The findings are completely different in groups with high blood pressure as the prevalence falls in the two highest age groups. This is shown in Fig. 7.10 and is seen in both sexes whether the material is classified by systolic or diastolic pressure.

From the literature available it does not appear that this difference in the influence of age has been noticed by others.

The low prevalence in the two highest age groups with high blood pressure can



possibly be explained by the fact that the individuals with hypertension and coronary disease die at an earlier age than those with normal blood pressure. The increased prevalence in the middle age groups (40-49 and 50-59 years) in both sexes could also indicate that coronary atherosclerosis develops earlier in individuals with hypertension. Thus these findings are in agreement with the pathologic-anatomical studies of Bell & Clawson (19), Davis & Kliner (46) the clinical series of Brown and co-workers (33) and also the Framingham study (48).

It also appears from Block, Crumpacker, Dry & Gage's (27) prognostic study of angina pectoris (see p. 152) that the severity of the hypertension as judged from the changes in the optic fundi, determines the prognosis. Thus the cases classified as fundus I give a survival rate of 32.1%, fundus II 17% and fundus III 1.3% while normal material (without hypertension) gives a rate of 40%.

The explanation of the increased occurrence of coronary disease in hypertension is based on the view that the high blood pressure increases the work of the heart, leading gradually to hypertrophy. Both the increased work and the hypertrophy of the heart cause an increase in the oxygen requirements of the myocardium. With this the possibility of symptoms of myocardial anoxia gradually increases, as the arteriosclerotic changes in the coronary vessels lead to reduction in the coronary blood flow. Thus hypertension leads indirectly to the development of coronary disease.

The influence of overweight varies in this series. The overweight groups are small in both the high and the low blood pressure groups. Most of the overweight persons are to be found in the age groups 50-59 and 60-69 years, and comparison of the whole series on a percentage basis can hardly be correct. But even if one chooses to analyse a 20-year age group (50-69) or a 30-year age group (40-69) with high blood pressure ( $\geq 105$  mm Hg diastolic)

one finds no difference in the prevalence rates in the overweight men and those of normal weight. There is, however, a higher prevalence of overweight in the low blood pressure group. On the other hand, the women show a higher prevalence of overweight both in the high and in the low blood pressure group.

The findings show a parallel to the symptom dyspnoea which also does not occur particularly frequently in overweight men (53 to 46% in the normal weight, compare p. 129) in the high blood pressure group.

This could indicate a sex difference in the heart disease among overweight individuals, but it is more likely that the difference in the prevalence may be ascribed to the higher refusal rate among the men (see p. 32).

It should be noted that this series has been based on the weight alone without regard to the fat level judged clinically. Overweight and fat are not identical even though many studies consider them to be equivalent. Thus many athletes can be overweight and yet not fat and conversely many people can be fat, but not overweight. The norms for overweight are based on the data given previously on page 122. A comparison between fat and overweight will be undertaken in a separate investigation.

It should also be noted that in this study no systematic estimations of the blood cholesterol were made. According to the Framingham study among others, it has been found that "hypercholesterolaemia" was also highly associated with the development of new coronary heart disease in men of age 45-62. Therefore the possibility that effects of this type are concealed in this series cannot be excluded.

Finally the prevalence of myocardial infarction is very low as only 19 individuals showed definite signs of a previous infarct.

It is possible that, among the 1350 individuals there are some cases who have returned to full health with return to normal of the electrocardiogram after an

undiagnosed infarction. Other individuals may have had a previous infarction, but this may have been masked by signs of hypertrophy and other abnormalities on the ECG. In general the electrocardiogram can be considered to be a fairly reliable diagnostic method with regard to acute infarct. Thus Roberts (191) states that a routine hospital electrocardiogram diagnoses about 80 per cent. of all acute myocardial infarctions. The electrocardiographic method is considerably less accurate in the cases where the electrocardiogram showed abnormalities beforehand. In this series the diagnosis has also been based on the history and in most cases there was good agreement between the clinical and electrocardiographic findings. A few exceptions occurred in elderly women.

One, with senile dementia (67 years) showed definite ECG changes without the characteristic symptomatology and one (79 years) presented marked dyspnoea at rest and pronounced asthenia without preceding symptoms pointing to myocardial disease.

However the most probable cause for the low prevalence of myocardial infarction in this series is selection due to non-attendance.

In chapters III and V an account is given of the attendance rate for the mass radiography as well as for this investigation. Both investigations required personal attendance. It must therefore be expected that the attendance of the individuals with previous infarcts will be particularly low because of their reduced physical capacity. Finally the individuals who could give a certificate from their doctors were not compelled to attend the mass radiological examination (see Bøe, Humerfelt & Wedervang, p. 43 Table 3.1). It has not been possible to check up on these certificates.

In other words the most healthy section of the population was investigated. The attendance of the men was worse than that

of the women throughout. This may be reflected in the prevalence of myocardial infarction in the two sexes and also in the total prevalence of coronary disease.

One must therefore make certain reservations in connection with the usefulness of the series in the elucidation of the prevalence of coronary disease, and great caution must be observed when making comparisons with other prevalence studies.

However even if one makes reservations on this point, the analyses of the series have brought out some interesting facts, which in part confirm earlier reports and also raise new questions.

We know little of the exact prevalence of coronary disease in the population or in groups of it. In order to give an idea of the dimensions of this problem Morris (155) in connection with an investigation in England of the 60-64 age group in men, states: About two-thirds have material amounts of coronary atherosclerosis; about a third have noteworthy stenosis in a main coronary artery. About 15% have ischaemic scars in the myocardium; about 5 per cent. have clinical coronary heart disease. That is to say: the manifest clinical disease is but the visible tip of the iceberg and we are dealing with a mass disorder on the scale of the epidemics of history.

## Summary

In this chapter the clinical manifestations of angina pectoris and myocardial infarction are studied in relation to the influence of sex, age, the height and lability of the blood pressure, and overweight.

The over-all prevalence of coronary disease is 6.5% in men and 8.5% in women (the ratio men: women is 1:1.3). When all the individuals with secondary hypertension and renal disease are excluded the prevalence becomes 6.3% in men and 7.6% in women (1:1.2). When the overweight persons are also removed the prevalence is 5.5% in men and 7.1% in women (1:1.3).

When dividing the series according to age and blood pressure a characteristic trend is seen. In the groups with low blood pressure (BP  $\leq 100$  mm diastolic or  $\leq 175$  mm systolic) an increase in the prevalence with rising age is seen in both sexes (Fig 7.10). In the groups with high blood pressure (BP  $\geq 105$  mm diastolic or  $\geq 180$  mm systolic) the total prevalence is two to three times greater than in groups with low pressure. However the prevalence in the two highest age groups is lower than in the preceding 50-59 year group.

The prevalence of coronary disease among the overweight individuals is greater than in those who are not overweight in both the high and low blood pressure groups in women. In men this trend is only seen in the low blood pressure group.

The total prevalence of myocardial infarction is slightly higher in the high blood pressure group 3.0% in men and 1.6% in women compared to 1.6% and 0.7% respectively in the low blood pressure

group. When dividing the series into age groups no significant trend can be seen. On the whole the infarct series is so small that no conclusions can be drawn.

The prevalence of coronary disease in this series shows a ratio men/women of 1/1.3. Thus there is a considerable difference in the sex distribution in this morbidity study in comparison to many other morbidity, mortality and pathologico-anatomical studies.

The reasons for this difference are discussed.

The most probable cause of the low prevalence in men is the higher refusal rate among the men. Individuals who could give a certificate from their doctor were not compelled to attend the mass radiography (see chapter III). In other words the most healthy section of the population has been investigated.

One must therefore make reservations as to the validity of the prevalence rates and proceed with caution when making comparisons with other studies.

## The cardiac findings

### I The size of the heart judged physically

A survey of the pathogenesis of the hypertrophy of the heart in hypertension has been given on page 114.

This hypertrophy affects the left ventricle in the first place but gradually as heart failure develops, dilatation occurs, first of the left ventricle with increasing functional mitral insufficiency, then of the left atrium. Afterwards enlargement of the right side of the heart appears with right ventricular hypertrophy and dilatation. The right atrium will also show dilatation if the heart failure is present for long enough. Thus the right side of the heart is unaffected in the early stages of the illness, but when left ventricular failure occurs the pressure in the pulmo-

nary artery will rise and the right ventricle will hypertrophy.

It is very difficult to differentiate between hypertrophy and dilatation of the heart clinically. The term cardiac enlargement is used instead since it covers both.

The clinical judgment of the size of the heart is based mainly on physical and radiological investigations.

The physical estimate is rough but in those cases where the apex of the heart is palpable and there is no deformity of the thorax or mediastinal shift the localization and the character of the apex beat can give fairly reliable information. Palpation of the apex beat is much more reliable in estimating the size of the heart than percussion of the cardiac dullness. Old age, adiposity and emphysema of the lungs are

factors which prevent one from feeling the apex beat. In these cases the size of the heart can only be determined by radiological methods.

The available literature shows great divergence with regard to the proportion of apex beats than can be localized by palpation. Niehaus & Wright (163) examined 1 000 normal subjects and found that the apex beat was definitely visible and/or palpable (erect, prone, or only leaning forward) in 24%, while Eve (65) recorded an impalpable apex beat in only one out of 70 young men examined. Isaac & Levy (104) localized the apex in 395 out of 500 recumbent men. According to these authors the apex beat is easier to determine in younger people, in those of lighter weight, and in women. Mainland & Gordon (138) found among 86 young adult men that the apex beat was impalpable or indefinite in about 5% when erect, in over one-third when recumbent.

The commonly used definition of the apex beat employs the farthest inferolateral point of maximal impulse. Isaac & Levy found 8.9 cm (3.5 in.) from the midsternal line as the most frequent position for the apex beat in their series. Mainland & Gordon found the mean position of the normal male apex beat 8.3 cm in 53 recumbent subjects. The estimated normal range (2 x standard deviation) was 6.4 to 10.2 cm.

According to White (233) the average position of the apex beat in normal adults is 8-8 1/2 cm to the left of the midsternal line, varying from 7-10 cm with extremes of body size. An apex beat 10 cm or more from the midsternal line can be considered to be pathological (see Friedberg 76).

In this series the size of the heart has been estimated systematically from the localization and character of the apex beat. The method used is in accordance with the general principles laid down by the American Heart Association, with the measurements taken in the frontal plane from the midline to the lateral point of maximal apical impulse. All measurements

were taken with the patient lying on his back. The location of the apex beat has been estimated to the nearest cm and the findings grouped in the following way

- I Apex beat up to and at 8 cm from the midline.
- II » » 9 cm from the midline.
- III » » 10 cm or more from the midline (displaced)

#### a) The localization of the apex beat

As was expected, the apex beat could not be located so frequently in old age, as in youth. This can be seen on classifying the

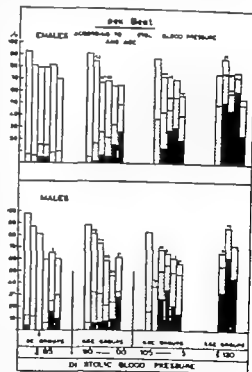


Fig 7.11 The Figure shows that the frequency of palpable apex beat decreases with age and further that the frequency of displacement of the apex beat increases with age and blood pressure. White rectangles: apex beat within 8 cm from mid-sternal line. Hatched rectangles: apex beat 9 cm from mid-sternal line. Black rectangles: apex beat 10 cm or more from mid-sternal line.

When dividing the series according to age and blood pressure a characteristic trend is seen. In the groups with low blood pressure (BP  $\leq 100$  mm diastolic or  $\leq 175$  mm systolic) an increase in the prevalence with rising age is seen in both sexes (Fig 7 10). In the groups with high blood pressure (BP  $\geq 105$  mm diastolic or  $\geq 180$  mm systolic) the total prevalence is two to three times greater than in groups with low pressure. However the prevalence in the two highest age groups is lower than in the preceding 50-59 year group.

The prevalence of coronary disease among the overweight individuals is greater than in those who are not overweight in both the high and low blood pressure groups in women. In men this trend is only seen in the low blood pressure group.

The total prevalence of myocardial infarction is slightly higher in the high blood pressure group 3 in men and 16 in women compared to 16% and 07% respectively in the low blood pressure

group. When dividing the series into age groups no significant trend can be seen. On the whole the infarct series is so small that no conclusions can be drawn.

The prevalence of coronary disease in this series shows a ratio men/women of 1:1.3. Thus there is a considerable difference in the sex distribution in this morbidity study in comparison to many other morbidity, mortality and pathologico-anatomical studies.

The reasons for this difference are discussed.

The most probable cause of the low prevalence in men is the higher refusal rate among the men. Individuals who could give a certificate from their doctor were not compelled to attend the mass radiography (see chapter III). In other words the most healthy section of the population has been investigated.

One must therefore make reservations as to the validity of the prevalence rates and proceed with caution when making comparisons with other studies.

## The cardiac findings

### I The size of the heart judged physically

A survey of the pathogenesis of the hypertrophy of the heart in hypertension has been given on page 114.

This hypertrophy affects the left ventricle in the first place but gradually as heart failure develops, dilatation occurs, first of the left ventricle with increasing functional mitral insufficiency then of the left atrium. Afterwards enlargement of the right side of the heart appears with right ventricular hypertrophy and dilatation. The right atrium will also show dilatation if the heart failure is present for long enough. Thus the right side of the heart is unaffected in the early stages of the illness, but when left ventricular failure occurs the pressure in the pulmo-

nary artery will rise and the right ventricle will hypertrophy.

It is very difficult to differentiate between hypertrophy and dilatation of the heart clinically. The term cardiac enlargement is used instead, since it covers both.

The clinical judgment of the size of the heart is based mainly on physical and radiological investigations.

The physical estimate is rough, but in those cases where the apex of the heart is palpable and there is no deformity of the thorax or mediastinal shift the localization and the character of the apex beat can give fairly reliable information. Palpation of the apex beat is much more reliable in estimating the size of the heart than percussion of the cardiac dullness. Old age, adiposity and emphysema of the lungs are

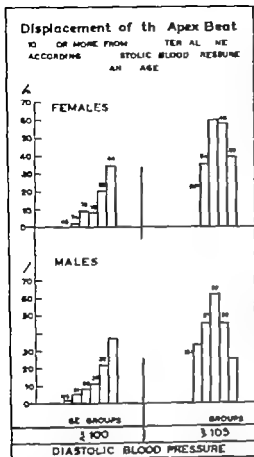


Fig 7.12 The individuals with displacement of the apex beat (10 cm or more) have been placed in 2 blood pressure groups. In the groups  $\leq 100$  mm the frequency increases evenly with age. In the groups  $\geq 105$  mm the frequency decreases in the 2 highest age groups, most markedly in men.

tolic classification of the series has been left out owing to lack of space.)

The frequency of displacement of the apex beat increases with age in both sexes. This is evident from Table 7.17 where the individuals in whom the apex beat was palpable 10 cm or more from the midline have been grouped. The effect however is not as marked in all the blood pressure groups, but is most evident in the blood pressure groups of under 100 mm Hg

diastolic except in the women in the blood pressure group of  $\leq 85$  mm. In the groups with higher diastolic blood pressure (105-115 and  $\geq 120$ ) the findings are somewhat different, as the frequency of displacement of the apex beat in the eldest ( $\geq 70$  years, in part also 60-69 years in men) is less than in the preceding age group.

Thus when this grouped series is divided into 2 blood pressure groups only  $\leq 100$  and  $\geq 105$  mm Hg, this condition is illustrated clearly as in Fig 7.12.

In this figure the frequency of displacement of the apex has been calculated only for the part of the series presented in Table 7.17 in which the apex beat was palpable.

In the groups with a diastolic blood pressure  $\geq 105$  mm almost 60% of the women in the age groups from 50-69 years show displacement of the apex. In men the age group 50-59 years shows the same frequency whereas the 60-69 and  $\geq 70$  year groups show this less frequently.

The influence of age as well as of blood pressure seems to be similar in both sexes.

The  $\chi^2$  test gives the following results

Table 7.17 (b)

| Sex     | BP       | Age      |
|---------|----------|----------|
| Females | (2) 66.2 | (3) 15.3 |
|         | (2) 37.5 | (2) 3.0  |

In this and in Tables 7.18 (b), 7.21, 7.23 (b) and 7.26 the  $\chi^2$  test is concentrated without presenting the contingency tables. The figures in parentheses are the degrees of freedom.

The series has been grouped into 3 blood pressure groups ( $\leq 100$ , 103-115 and  $\geq 120$ ). In both sexes the 30 and 40 year groups have been combined into one. Thus in women a 3 times 4 and in men 3 times 3 grouping has been used for the analyses.

The analyses show a significant difference between the blood pressure groups in both sexes. The difference between the age groups, however, is only significant in women.

*Table 7 18. Displacement of apex beat in relation to blood pressure liability*

Number of individuals with maximal apical impulse 10 cm or more from midsternal line (+) compared to number of individuals in the different age- and blood pressure groups (%). The individuals in whom the apex beat was not palpable are omitted

| Diastolic BP  |            |     | Age groups |       |       |       |       |      | Total |          |
|---------------|------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|               |            |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| F males       |            |     |            |       |       |       |       |      |       |          |
| Sitting ≥ 105 |            | +   | 5          | 21    | 26    | 27    | 10    | 89   |       |          |
|               |            | No. | 2          | 21    | 55    | 45    | 37    | 28   | 198   | 45       |
| Resting       | Non labile | +   | 3          | 17    | 16    | 15    | 7     | 58   |       |          |
|               |            | No. | 1          | 11    | 36    | 30    | 26    | 15   | 117   | 50       |
|               | Labile     | +   | 2          | 4     | 10    | 12    | 3     | 31   |       |          |
|               |            | No. | 1          | 10    | 19    | 15    | 21    | 15   | 81    | 38       |
| Male          |            |     |            |       |       |       |       |      |       |          |
| Sitting ≥ 105 |            | +   | 9          | 15    | 9     | 1     | 36    |      |       |          |
|               |            | No. | 5          | 8     | 23    | 25    | 1     | 10   | 92    | 29       |
| Resting       | Non-labile | +   | 7          | 8     | 4     | 1     | 21    |      |       |          |
|               |            | No. |            | 5     | 13    | 12    | 12    | 4    | 46    | 27       |
|               | Labile     | +   | 2          | 7     | 5     |       | 15    |      |       |          |
|               |            | No. | 3          | 5     | 10    | 15    | 9     | 6    | 46    | 39       |

*The influence of the liability of the blood pressure*  
Using the same method as that given on page 133 an analysis has been made of the frequency of displacement of the apex beat in relation to the liability of the blood pressure.

Table 7 18 shows the frequency of displacement of the apex beat (10 cm or more) in the high blood pressure group (BP ≥ 105 mm diastolic) divided into a labile and a non-labile group. The findings are illustrated in Fig. 7 13.

Both the Table and the Figure show that there is a tendency towards an increased frequency of displacement of the apex beat in the non-labile group in comparison to the labile. The total prevalence in the non-labile group is thus, for men, 46 % as against 33 % in the labile. In women the corresponding figures are 50 % and 38.

However the  $\chi$  test does not show any significant difference between the labile

and non-labile blood pressure groups in the two sexes. On the other hand, there is a significant difference between the age groups in women.

*Table 7 18 (b)*

| Sex     | BP      | Age      |
|---------|---------|----------|
| Females | (1) 2.5 | (2) 6.0* |
| Males   | (1) 0.7 | (1) 2.5  |

In women 3 age groups (30-49 50-59 and 60 or higher) and in men 2 age groups (40-59 and 60 or higher) have been used for the analyses.

There is no difference in the frequency of displacement of the apex beat, in the labile and non-labile group, in the low blood pressure group (≤ 100 mm Hg diastolic). The total prevalence among these individuals is 6.9 % in the men, 7.3 % in the labile and 6.5 % in the non-labile. In women the corresponding figures

## Displacement of Apex Beat

ACCORDING TO BLOOD PRESSURE CATEGORY

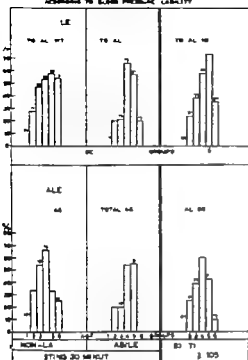


Fig 7.13. The Figure shows the tendency to greater frequency of displacement of the apex beat in the non-labile blood pressure groups in both sexes.

are almost identical (96.9, 97.7 and 96.6%). The Table is not included owing to lack of space. Thus the conditions are not unlike those found with the symptom of dyspnoea (see p. 135).

#### b) The character of the apex beat

The character of the apex beat is as important as the localization in the physical estimation of the size of the heart. Many cardiologists hold that a distinctly heaving apex beat is a much more definite sign of hypertrophy of the heart than displacement of the apex beat.

With a heaving apex beat the palpating finger or the palm of the hand is lifted markedly. This lifting can often be slug-

ish and of small amplitude and must not be confused with the abnormally prominent apex beat which can be found in individuals with a hyperactive heart.

A heaving apex beat, however, is not a constant finding in hypertrophy of the heart due to hypertension, as the finding varies in accordance with the age, obesity and pulmonary changes.

In this series the character of the apex beat has been judged by the criteria given above.

The total frequency of a heaving apex beat is relatively low. The series has therefore been divided into 2 blood pressure groups only ( $\leq 100$  mm and  $\geq 105$  mm diastolic or  $\leq 175$  and  $\geq 180$  systolic).

The frequency of a steady heaving apex beat shows an increase with age when the series is classified by the diastolic pressure (see Fig 7.14).

The frequency is greater in the blood pressure group  $\geq 105$  mm than in the blood pressure group  $\leq 100$  mm. The total frequencies are thus 18.7% and 2.4% in women and the corresponding figures for men are 8% and 1.4%. The

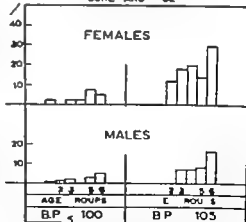
Steady Heaving Apex Beat  
ACCORDING TO DIASTOLIC BLOOD PRESSURE AND AGE

Fig 7.14 The steady heaving apex beat increases with age and blood pressure



There was no significant difference between the two groups in the number of patients who had a history of previous otitis media with effusion. The mean age of the patients in the high blood pressure group was 11.5 years (range 7-15 years) and in the low blood pressure group was 11.5 years (range 7-15 years). There was no significant difference between the two groups in the number of patients who had a history of previous otitis media with effusion.

## Summary

The results of the study show that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group.

The results also show that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group. The results also show that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group.

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There was no significant difference between the two groups in the number of patients who had a history of previous otitis media with effusion. The mean age of the patients in the high blood pressure group was 11.5 years (range 7-15 years) and in the low blood pressure group was 11.5 years (range 7-15 years).

There is a tendency toward an increase in frequency of otitis media with effusion in the non-labile group. However, this is not statistically significant.

The frequency of a hearing impairment is significantly lower in the high blood pressure group than in the low blood pressure group.

## If The muscular findings

The results of the study show that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group. The results also show that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group. The results also show that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group.

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Further analysis of the data showed that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group.

The results also show that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group. The results also show that the prevalence of otitis media with effusion is significantly higher in the high blood pressure group than in the low blood pressure group.

same authors the murmur over the base of the heart is due to a dilatation of the aorta. Friedberg (76) believes that these systolic murmurs are dependent on mitral or aortic sclerosis and calcification. In still more advanced cases a diastolic murmur can be heard over the aortic ostium, indicating relative insufficiency of the aortic valve. This regurgitation can only be heard when the blood pressure is considerably raised. Wood (238) says that it may be associated with diastolic pressures of 150 to 170 mm Hg.

Accentuation of the aortic sound is a usual auscultatory finding. This gradually takes the form of a high-pitched sound that is conducted out to the sides and up into the neck. This accentuation, however, is also an age phenomenon (see Harrison, 95). Here, too, the variation is great. Wohlferth and Margolies (237) state that the enormous variability of the sounds in patients with similar degrees of hypertension is most impressive.

Friedberg (76), Stroud & Stroud (224), White (233) and Wood (238) have given general reviews of the auscultatory findings in hypertension. Study of the literature available on hypertension shows that there are relatively few who have done any systematic work on the auscultatory findings. Janeway (105) found a marked accentuation of the second aortic sound proportionately more than twice as frequent in the deceased as in the living groups, and moderate accentuation was about equal the slighter degrees greatly preponderating in the living. This shows a rough correspondence with the median for the blood pressures of the two groups, as would be expected. Similarly Volhard & Fahr (730) have given a closer description of the objective heart findings. Ehrström (58) has also given a similar survey.

Recently Barlow & Kincaid-Smith (15) have performed a clinical and phonocardiographic study on one hundred consecutive hypertensive patients on whom the average casual blood pressure readings

exceeded 180/100 mm Hg. The patients were observed over a period of 18 months to 2 years. An aortic sound was present in at least 50 per cent, an ejection systolic murmur in 71 patients, while a regurgitant systolic murmur was present in only 2 patients. Nine cases had an early aortic diastolic murmur. The aortic component of the second sound was louder than normal in 81 per cent.

Studies of the literature have shown that certain characteristic auscultatory findings can be noticed in hypertensive heart disease. This series shows all degrees of raised blood pressure in the different age groups with and without hypertensive heart disease. It is therefore reasonable to view the results of earlier observations in the light of the hypothesis given on p. 121.

#### a) *The first heart sound*

##### 1. *Accentuation of the first heart sound*

A louder accentuated first heart sound was found in relatively few individuals. Thus of the reduced series (Table 7-1 subgroup 2) it was found in 9% of the women and 7% of the men. The frequency is on the whole greatest in the younger age groups, and in the women considerably higher in the groups with high blood pressure.

Thus the total findings in women are 16 in the blood pressure group  $\geq 105$  mm compared with 5.2 in the group  $\leq 100$  mm Hg diastolic. The difference between these two blood pressure groups is greatest in the 30-39 year group (21% compared with 8%) otherwise the difference decreases with increasing age.

In men on the other hand, there is no relationship with blood pressure. Here also an accentuated first heart sound is commoner in the younger age groups. It is present in 12% of the 15-29 group, and decreases evenly to 4% between 50-59 years of age. The frequency is again somewhat higher (7-8%) in the two highest age groups.



Table 7.19 Apical systolic murmur

Number of individuals with moderate (+) and loud (++) systolic murmur compared to number of individuals in the different age and blood pressure groups (No.)

| Diastolic BP |     | Age groups |       |       |       |       |      | Total |          |
|--------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|              |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| F male       |     |            |       |       |       |       |      |       |          |
| ≤ 85         | +   | 2          | 6     | 5     | 7     | 2     | 2    | 22    | 21/2     |
|              | ++  |            |       | 1     |       |       | 1    | 2     |          |
|              | No. | 13         | 31    | 19    | 19    | 11    | 10   | 103   |          |
| 90-100       | +   | 2          | 13    | 23    | 21    | 28    | 26   | 113   | 29/2.5   |
|              | ++  |            | 1     |       | 3     | 2     | 4    | 10    |          |
|              | No. | 34         | 53    | 95    | 86    | 71    | 57   | 396   |          |
| 105-115      | +   |            | 7     | 11    | 18    | 18    | 11   | 65    | 38/9     |
|              | ++  |            | 1     | 1     |       | 4     | 9    | 15    |          |
|              | No. | 1          | 16    | 44    | 40    | 40    | 30   | 171   |          |
| ≥ 120        | +   |            | 2     | 9     | 17    | 15    | 5    | 49    | 45/8     |
|              | ++  |            |       | 1     | 4     | 2     | 2    | 9     |          |
|              | No. |            | 4     | 25    | 35    | 26    | 20   | 110   |          |
| Total        | +   | 4          | 28    | 47    | 63    | 63    | 44   | 249   | 32/4.6   |
|              | ++  |            | 2     | 3     | 7     | 8     | 16   | 36    |          |
|              | No. | 48         | 104   | 183   | 180   | 148   | 117  | 780   |          |
| M 1          |     |            |       |       |       |       |      |       |          |
| ≤ 85         | +   | 4          | 4     | 2     | 4     | 3     | 1    | 18    | 13/3     |
|              | ++  | 1          |       |       | 1     |       | 2    | 4     |          |
|              | No. | 48         | 33    | 16    | 15    | 12    | 10   | 134   |          |
| 90-100       | +   | 8          | 9     | 7     | 10    | 10    | 7    | 51    | 15/0.9   |
|              | ++  |            |       | 1     |       | 1     | 1    | 3     |          |
|              | No. | 88         | 76    | 64    | 46    | 50    | 21   | 345   |          |
| 105-115      | +   | 1          | 1     | 4     | 6     | 4     | 9    | 25    | 24/2     |
|              | ++  |            |       |       | 2     |       |      | 2     |          |
|              | No. | 6          | 8     | 22    | 23    | 23    | 1    | 103   |          |
| ≥ 120        | +   |            | 1     | 1     | 2     | 5     | 2    | 11    | 23/2     |
|              | ++  |            | 1     |       |       |       |      | 1     |          |
|              | No. |            | 3     | 18    | 16    | 11    | 3    | 51    |          |
| Total        | +   | 13         | 13    | 14    | 22    | 22    | 19   | 105   | 1/1.6    |
|              | ++  | 1          | 1     | 1     | 3     | 1     | 3    | 10    |          |
|              | No. | 142        | 120   | 170   | 100   | 96    | 55   | 633   |          |

frequency in the groups with high blood pressure. In men there is no relationship to blood pressure.

Gallop rhythm occurs more often in

groups with high blood pressure. The few cases of gallop rhythm in the groups with low blood pressure occur only in the highest age groups.

Table 7.20. *Apical systolic murmur*

Number of individuals with moderate (+) and loud (++) systolic murmur compared to number of individuals in the different age and blood pressure groups (No.)

| Systolic BP |     | Age groups |       |       |       |       |      | Total |          |
|-------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|             |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Female      |     |            |       |       |       |       |      |       |          |
| ≤ 145       | +   | 2          | 4     | 3     | 7     | 3     | 1    | 20    | 14       |
|             | ++  |            |       | 1     |       |       | 1    | 2     |          |
|             | No. | 28         | 39    | 30    | 27    | 14    | 8    | 146   |          |
| 150-175     | +   | 2          | 20    | 1     | 15    | 16    | 3    | 60    | 7        |
|             | ++  |            |       | 1     | 1     | 1     |      | 3     |          |
|             | No. | 20         | 33    | 89    | 72    | 42    | 20   | 296   |          |
| 180-205     | +   |            | 3     | 11    | 3     | 23    | 3    | 87    | 43       |
|             | ++  |            | 2     |       | 3     | 3     | 6    | 14    |          |
|             | No. |            | 11    | 35    | 47    | 55    | 53   | 201   |          |
| ≥ 210       | +   |            | 1     | 12    | 16    | 20    | 13   | 62    | 45       |
|             | ++  |            |       | 1     | 3     | 4     | 8    | 16    |          |
|             | No. |            | 1     | 29    | 34    | 37    | 36   | 137   |          |
| Total       | +   | 4          | 28    | 47    | 63    | 62    | 44   | 49    | 32       |
|             | ++  |            | 2     | 3     | 7     | 8     | 15   | 35    |          |
|             | No. | 48         | 104   | 183   | 180   | 148   | 117  | 780   |          |
| Male        |     |            |       |       |       |       |      |       |          |
| ≤ 145       | +   | 7          | 3     |       | 5     | 4     |      | 21    | 10       |
|             | ++  |            |       |       | 1     |       | 1    | 2     |          |
|             | No. | 63         | 54    | 38    | 27    | 18    | 8    | 210   |          |
| 150-175     | +   | 8          | 8     | 6     | 6     | 7     | 6    | 41    | 15       |
|             | ++  |            |       | 1     |       | 1     | 1    | 3     |          |
|             | No. | 71         | 36    | 48    | 36    | 38    | 18   | 267   |          |
| 180-205     | +   | 1          | 3     | 3     | 6     | 5     | 9    | 29    | 23       |
|             | ++  | 1          | 1     |       |       |       |      | 6     |          |
|             | No. | 6          | 9     | 21    | 24    | 24    | 21   | 105   |          |
| ≥ 210       | +   |            | 1     | 1     | 5     | 6     | 3    | 16    | 31       |
|             | ++  |            |       |       |       |       |      |       |          |
|             | No. |            | 1     | 13    | 13    | 16    | 8    | 51    |          |
| Total       | +   | 16         | 15    | 14    | 22    | 22    | 18   | 107   | 17       |
|             | ++  | 1          | 1     | 1     | 3     | 1     | 4    | 11    |          |
|             | No. | 142        | 120   | 170   | 100   | 96    | 55   | 633   |          |

The total number of cases with accentuation of the first heart sound and gallop rhythm is so low that statistical evaluation is not possible.

*b) Systolic murmur over the apex*

The murmur was of relatively short duration in the reduced series (Table 71 subgroup 2) and in most cases was of

ejection character a few were of the pan systolic regurgitant type. When analysing the series these two types have been combined.

The intensity of systolic murmurs over the apex is expressed by graduation as observed by Levine (121). In grouping this series the following two classifications have been used: moderate systolic murmurs, comprising Levine's grades 2-3 and 3; and loud comprising grades 3-4, 4 or higher.

The frequency of moderate and loud systolic murmurs in this purged series appears from Tables 7.19 and 7.20 and the findings are illustrated in Fig. 7.13.

In the groups with low blood pressure (diastolic  $\leq 100$  mm or systolic  $\leq 175$  mm Hg) the influence of age can be seen distinctly in both sexes. The influence of age seems to be even, with the exception of women with a moderate systolic murmur in the blood pressure group  $\leq 175$  mm Hg. In men the frequency of moderate systolic murmurs increases from about 10% in the youngest to between 30-35% in the highest age groups in both classifications. In women the frequency increases to about 50% in the highest age groups classified by diastolic pressure.

The influence of age is similar with loud systolic murmurs, but the occurrence is on the whole low and they do not occur in the youngest age groups in either sex. The frequency increases evenly from the 40-49 year group to between 4% and 10% in the highest age group according to both classifications.

In the groups with high blood pressure (diastolic  $\geq 105$  or systolic  $\geq 180$  mm)

the frequency of moderate systolic murmurs is markedly higher in both sexes and according to both classifications. However the difference in the frequency between the groups with high and low blood pressure is not so marked in men on classification by diastolic pressure.

Loud systolic murmurs occur more often in the women with high than in those with low blood pressure. The increase with age seen in the groups with low pressure can only be seen on classification by diastolic pressure.

The occurrence in men is too irregular and too low to enable one to draw any conclusions.

The statistical analyses of all apical systolic murmurs have been performed on the series presented in Tables 7.19 and 7.20.

In both sexes in both classifications 3 age groups (30-49, 50-59 and 60 or higher) have been used. In women 4 blood pressure groups are used while in men 3 blood pressure groups are used ( $\leq 85$ , 90-100 and  $\geq 105$  diastolic, or  $\leq 145$ , 150-175, and  $\geq 180$  systolic).

The  $\chi^2$  test (Table 7.21) shows a statistically significant difference between the blood pressure and age groups in women in both classifications. In men a similar significant difference is seen, except for the difference between the blood pressure groups on classification by diastolic pressure.

#### *The influence of the lability of the blood pressure*

On dividing the series into labile and non-labile groups (see p. 133) little difference is found between the groups.

Table 7.21

| Sex     | Systolic |          | Diastolic |           |
|---------|----------|----------|-----------|-----------|
|         | BP       | Age      | BP        | Age       |
| Females | (3) 47.7 | (2) 7.9* | (3) 21.6  | (2) 10.6* |
| Males   | (2) 10.3 | (2) 8.9* | (2) 1.4   | (2) 13.9* |

In men in the group  $\geq 103$  mm Hg the total frequency of systolic murmurs is thus 32 in the non labile groups compared

with 27 in the labile groups. In women the corresponding figures are 46 and 40. There is no difference in the group  $\leq 100$  mm Hg either the percentage in men being 16 and 15 and in women 31 and 29 in the corresponding non labile and labile groups.

### Summary

Systolic murmur over the apex is influenced by age and blood pressure.

The murmurs have been graded into moderate (comprising Levine's grades 2, 3 and 3+) and loud (comprising grades 3+ 4 or higher). The frequency of the murmurs is markedly greater in women.

Statistical analysis of all apical systolic murmurs shows a significant difference between the blood pressure groups and the age groups in women in both the systolic and diastolic classification of the series. In men the similar significant difference is seen except for the difference

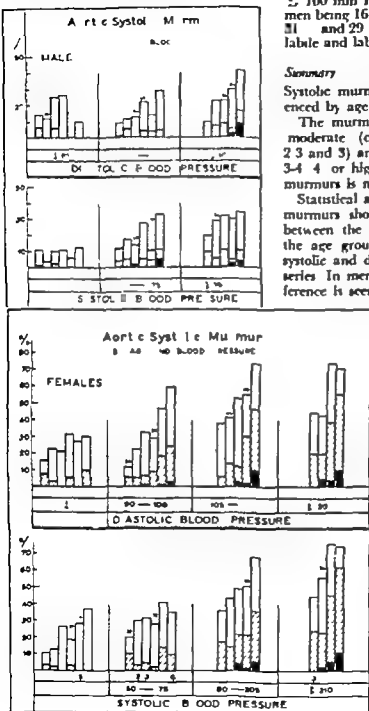


Fig 7.16. The Figure shows the increase in aortic systolic murmurs with age and blood pressure in women. In men the frequency is less, but the same trend with increasing age is seen except for the groups  $> 145$  mm systolic and  $< 85$  mm diastolic. White rectangles denote moderate systolic murmur. Hatched rectangles denote loud systolic murmur. Black rectangles denote very loud systolic murmur.

between the blood pressure groups on classification by diastolic pressure.

On dividing the series into labile and non-labile groups little difference is found in the frequency of systolic murmurs.

c) *Systolic murmurs over the base of the heart (aortic systolic murmur)*

The systolic murmurs over the base of the heart were of an ejection character and have been graded in the following way

- 1 Moderate systolic murmur
- 2 Loud (rough or blowing) systolic murmur
- 3 Very loud (stenotic 'sawing') systolic murmur

The calculations have been made on the reduced series (Table 7.1 subgroup 2)

The frequency of these murmurs shows almost the same pattern as the apical systolic murmurs an increase with age and increasing blood pressures in both sexes.

The frequency of these murmurs is markedly greater in women. This is apparent from Tables 7.22 and 7.23 and also from Fig 7.16.

Here the total frequency of all grades of murmurs rises from 15% in the youngest age group to 37% in the oldest when the diastolic blood pressure is  $\leq 85$  and from 10% to 37% with a systolic blood pressure  $\leq 145$  mm. The increase with age is even more marked in the higher blood pressure groups.

The frequency in the same age group increases with rising blood pressure. Thus the frequency of all murmurs in the 40-49 age group shows an increase from 21% in the group with a diastolic blood pressure  $\leq 85$  to 44% in the group  $\geq 120$  mm Hg. On classification of the series by the systolic pressure the corresponding figures are 26% in the lowest and 45% in the highest blood pressure group. In the highest age group the corresponding figures are 31% and 70% on classification

by the diastolic pressure and 37% and 75% when using the systolic pressure.

The frequency of loud and very loud systolic murmurs is similarly influenced by age and blood pressure.

In men the frequency is markedly less than in women, so the series has been grouped into 3 blood pressure groups in both classifications (see Fig 7.16)

Here one sees a tendency to increase in frequency with increasing age, except for the groups  $\leq 145$  mm systolic and  $\leq 85$  mm diastolic. The occurrence of the loud and very loud systolic murmurs is too irregular to allow any conclusions to be drawn. The increase with higher age and blood pressure is much less pronounced.

The statistical analysis was first performed on all grades of aortic systolic murmurs.

The cells within the series have been combined to give 3 age groups in women (30-49, 50-59 and 60 or higher) keeping the 4 blood pressure groups as in the two Tables. In men it has been necessary to combine the blood pressure groups also, giving two ( $\leq 100$  and  $\geq 105$  mm diastolic or  $\leq 175$  and  $\geq 180$  mm systolic) blood pressure groups.

The  $\chi^2$  test shows a highly significant difference between the blood pressure and age groups in women. In men there is no significant difference between the age groups (compare Table 7.23 (b) p. 172)

Secondly the same analyses have been made of those in the loud and very loud grades.

It has been necessary to combine the groups further. In women in the diastolic classification only two BP groups ( $\leq 100$ ,  $\geq 105$ ) and 4 age groups (below 40 years) have been used. In men there are too few individuals to make a two-way classification.

The results show a significant difference between the age and blood pressure groups in women in both classifications.



Table 7.22 Aortic systolic murmur

Number of individuals with moderate (+) load (++) or very load (+++) systolic murmur compared to the number of individuals in the different age and blood pressure groups (No.)

| Systolic BP |     | Age groups |       |       |       |       |      | Total |          |
|-------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|             |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Female      |     |            |       |       |       |       |      |       |          |
| ≤ 145       | +   |            | 4     | 8     | 4     | 4     | 3    | 25    | 17.2     |
|             | ++  | 1          | 1     |       | 1     |       |      | 3     |          |
|             | +++ |            |       |       |       |       |      |       |          |
|             | No. | 28         | 39    | 30    | 27    | 14    | 8    | 146   |          |
| 150-175     | +   | 2          | 14    | 24    | 18    | 11    | 5    | 74    | 5.6      |
|             | ++  | 2          | 2     | 4     | 2     | 6     | 2    | 18    |          |
|             | +++ |            |       |       |       |       |      |       |          |
|             | No. | 20         | 33    | 89    | 72    | 4     | 20   | 206   |          |
| 180-205     | +   |            |       | 9     | 13    | 16    | 17   | 57    | 2.3      |
|             | ++  |            | 2     | 5     | 8     | 11    | 16   | 42    |          |
|             | +++ |            |       | 1     | 2     | 1     | 3    | 7     |          |
|             | No. |            | 11    | 35    | 47    | 55    | 53   | 201   |          |
| ≥ 210       | +   |            |       | 6     | 11    | 11    | 8    | 36    | 2.6      |
|             | ++  |            |       | 7     | 7     | 15    | 15   | 44    |          |
|             | +++ |            |       | 1     | 1     | 2     | 4    | 8     |          |
|             | No. |            | 1     | 29    | 34    | 37    | 36   | 137   |          |
| Total       | +   | 4          | 20    | 47    | 46    | 42    | 33   | 192   | 25.14    |
|             | ++  | 3          | 3     | 16    | 18    | 32    | 33   | 107   |          |
|             | +++ |            |       |       | 3     | 3     | 7    | 13    |          |
|             | No. | 48         | 104   | 183   | 180   | 148   | 117  | 780   |          |

## Male

|         |     |     |     |     |     |    |    |     |      |
|---------|-----|-----|-----|-----|-----|----|----|-----|------|
| ≤ 145   | +   | 6   | 2   | 3   | 3   | 1  | 1  | 16  | 8.1  |
|         | ++  | 1   |     | 1   |     |    |    | 2   |      |
|         | +++ |     |     |     |     |    |    |     |      |
|         | No. | 65  | 54  | 38  | 27  | 18 | 8  | 190 |      |
| 150-175 | +   | 5   | 7   | 6   | 8   | 2  | 4  | 32  | 1.4  |
|         | ++  | 2   | 3   | 1   | 2   | 2  | 1  | 11  |      |
|         | +++ |     |     |     |     |    | 1  | 1   |      |
|         | No. | 71  | 56  | 48  | 36  | 38 | 18 | 268 |      |
| 180-205 | +   |     | 1   | 6   | 5   | 4  | 8  | 22  | 2.7  |
|         | ++  |     | 1   | 2   | 2   |    | 2  | 7   |      |
|         | +++ |     |     |     |     |    | 1  | 1   |      |
|         | No. | 6   | 9   | 31  | 24  | 24 | 21 | 105 |      |
| ≥ 210   | +   |     |     | 2   | 3   | 6  | 1  | 12  | 2.6  |
|         | ++  |     |     |     | 2   | 1  |    | 3   |      |
|         | +++ |     |     |     |     | 1  |    | 1   |      |
|         | No. |     | 1   | 13  | 13  | 16 | 8  | 51  |      |
| Total   | +   | 11  | 10  | 17  | 19  | 13 | 12 | 82  | 13.4 |
|         | ++  | 3   | 4   | 4   | 6   | 3  | 3  | 23  |      |
|         | +++ |     |     |     |     | 1  | 2  | 3   |      |
|         | No. | 142 | 120 | 120 | 100 | 96 | 55 | 633 |      |

Table 7.23. Aortic systolic murmur

Number of individuals with moderate (+) loud (++) or very loud (+++) systolic murmur compared to the number of individuals in the different age and blood pressure groups (No.)

| Diastolic BP |     | Age groups |       |       |       |       |      | Total |               |
|--------------|-----|------------|-------|-------|-------|-------|------|-------|---------------|
|              |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent      |
| Females      |     |            |       |       |       |       |      |       |               |
| ≤ 85         | +   | 1          | 6     | 4     | 5     | 3     | 2    | 21    | 20<br>4       |
|              | ++  | 1          | 1     |       | 1     |       | 1    | 4     |               |
|              | +++ |            |       |       |       |       |      |       |               |
|              | No. | 15         | 31    | 19    | 19    | 11    | 10   | 105   |               |
| 90-100       | +   | 2          | 9     | 25    | 17    | 20    | 20   | 93    | 23<br>11<br>1 |
|              | ++  | 2          | 3     | 5     | 8     | 12    | 12   | 42    |               |
|              | +++ |            |       |       |       | 1     | 2    | 4     |               |
|              | No. | 34         | 55    | 95    | 86    | 71    | 57   | 396   |               |
| 105-115      | +   | 1          | 5     | 12    | 16    | 10    | 8    | 52    | 30<br>19<br>3 |
|              | ++  |            | 1     | 8     | 4     | 11    | 11   | 35    |               |
|              | +++ |            |       |       | 1     | 1     | 3    | 5     |               |
|              | No. | 1          | 16    | 44    | 40    | 40    | 30   | 171   |               |
| ≥ 120        | +   |            |       | 6     | 8     | 9     | 3    | 26    | 24<br>26<br>5 |
|              | ++  |            |       | 5     | 5     | 9     | 9    | 28    |               |
|              | +++ |            |       |       | 2     | 1     | 2    | 5     |               |
|              | No. |            | 4     | 25    | 35    | 26    | 20   | 110   |               |
| Total        | +   | 4          | 20    | 47    | 46    | 42    | 33   | 192   | 25<br>14<br>2 |
|              | ++  | 3          | 5     | 16    | 18    | 32    | 33   | 107   |               |
|              | +++ |            |       | 1     | 3     | 3     | 7    | 14    |               |
|              | No. | 48         | 104   | 183   | 180   | 148   | 117  | 780   |               |
| Males        |     |            |       |       |       |       |      |       |               |
| ≤ 85         | +   | 4          | 4     | 3     | 4     |       | 1    | 16    | 12<br>2       |
|              | ++  | 2          |       | 1     |       |       |      | 3     |               |
|              | +++ |            |       |       |       |       |      |       |               |
|              | No. | 48         | 33    | 16    | 15    | 12    | 10   | 134   |               |
| 90-100       | +   | 7          | 5     | 8     | 8     | 5     | 5    | 38    | 11<br>3       |
|              | ++  | 1          | 4     |       | 8     | 2     | 1    | 10    |               |
|              | +++ |            |       |       |       |       |      |       |               |
|              | No. | 88         | 76    | 64    | 46    | 50    | 21   | 345   |               |
| 105-115      | +   |            | 1     | 4     | 4     | 4     | 8    | 19    | 19<br>8       |
|              | ++  |            |       | 3     | 3     | 1     | 1    | 8     |               |
|              | +++ |            |       |       |       |       | 2    | 2     |               |
|              | No. | 6          | 8     | 22    | 23    | 23    | 21   | 103   |               |
| ≥ 120        | +   |            |       | 2     | 3     | 4     |      | 9     | 18<br>4       |
|              | ++  |            |       |       | 1     |       | 1    | 2     |               |
|              | +++ |            |       |       |       | 1     |      | 1     |               |
|              | No. |            | 3     | 18    | 16    | 11    | 3    | 51    |               |
| Total        | +   | 11         | 10    | 17    | 19    | 15    | 12   | 82    | 13<br>4       |
|              | ++  | 3          | 4     | 4     | 6     | 3     | 3    | 23    |               |
|              | +++ |            |       |       |       | 1     | 2    | 3     |               |
|              | No. | 142        | 120   | 120   | 100   | 96    | 55   | 633   |               |

Table 7.23 (b) Aortic systolic murmur

| Sex              | Systolic |           | Diastolic |          |
|------------------|----------|-----------|-----------|----------|
|                  | BP       | Age       | BP        | Age      |
| All grades       |          |           |           |          |
| Females          | (3) 46.4 | (2) 13.9* | (3) 21.7  | (*) 21.1 |
| Males            | (1) 8.6  | (3) 3.1   | (1) 5.1   | (2) 3.9  |
| Loud & very loud |          |           |           |          |
| Females          | (2) 61.5 | (*) 14.4  | (1) 22.8  | (3) 34.3 |

### *The influence of the lability of the blood pressure*

The series has been investigated from the point of view of the lability of the blood pressure similar to that used for previous symptoms and signs (see p. 133).

It appears that in women with a blood pressure of  $\geq 105$  mm diastolic in a sitting position the total frequency of all systolic murmurs over the base of the heart is somewhat greater in the groups with non-labile blood pressure (51) compared with the labile groups (47). In the same way the frequency of loud and very loud systolic murmurs is greater in the non-labile groups (28) than in the labile (20). The difference is somewhat more prominent in the younger age groups than in the older. Thus in the 30-39 age group the frequency = 36 in the non-labile groups and 0 in the labile. In the 40-49 age group it is 17 compared with 8 and in the 50-59 age group 17 compared with 9.

The difference between the non-labile and labile blood pressure groups is not statistically significant ( $\chi^2$  all grades 0.8 and loud and very loud 1.6 on 1 d.f.).

Between the age groups there is a highly significant difference. In the groups with low blood pressure ( $< 100$  mm Hg) in a sitting position the frequency is practically the same in the non-labile and labile groups. Thus all the systolic murmurs occur in 33 of both groups, loud and very loud systolic murmurs appear in 11 of the non-labile and 9 of the labile.

In men the frequency of the systolic murmur is so low that the series cannot be evaluated.

### *Summary*

Aortic systolic murmurs were of an ejection character and have been graded into moderate loud and very loud murmurs.

The frequency of the murmurs shows almost the same pattern as the apical systolic murmurs: an increase with age and blood pressure in both sexes. This is seen on both systolic and diastolic classification of the series. The total frequency of all grades is nearly twice as high in women (Fig. 7.16).

The  $\chi^2$  test on all grades of aortic systolic murmurs shows a highly significant difference between the blood pressure and age groups in women. In men there is no significant difference between the age groups (Table 7.23 (b)).

The same analysis of those with loud and very loud grades shows a significant difference between the blood pressure and age groups in women on both classifications. For men there are too few individuals to make a two-way classification.

The frequency of all grades of loud and very loud murmurs is slightly but not significantly greater in the non-labile than in the labile groups in women.

### *d) Accentuation of the second aortic sound*

In this series the second aortic sound, as judged by auscultation, has been divided into two grades, depending upon the quality and harshness of the sound.

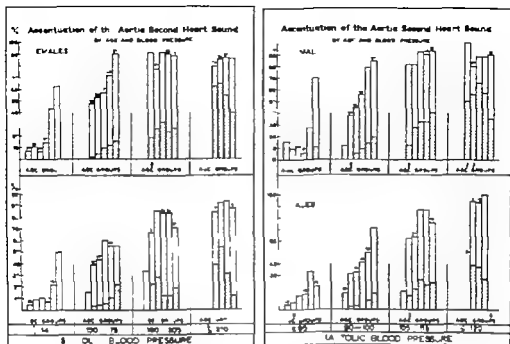


Fig 7.17 White rectangles slight accentuation of second aortic sound. Hatched rectangles marked. The figure shows the influence of age and blood pressure on the second heart sound. Marked accentuation is rare in the lower blood pressure groups.

- 1) Slight accentuation — without transmission.
- 2) Marked accentuation (roughening, ringing) heard over the base and transmitted to the sides.

The influence of age and blood pressure on the frequency of an accentuated aortic sound is similar in both sexes, as in the auscultatory findings mentioned earlier.

Slight accentuation of the aortic sound is markedly influenced by age in the groups with low blood pressures in both sexes, whether the series is classified by systolic or diastolic pressure. This is evident from Tables 7.24 and 7.25 and is illustrated in Figure 7.17.

In the groups with high blood pressure, on the other hand the frequency of slight accentuation of the aortic sound is about the same in all age groups, whether the

series is classified by systolic or diastolic pressure.

The frequency of accentuation of the aortic sound shows a pronounced increase with rising blood pressure, and this increase is greatest in the younger individuals. The frequency is thus 12% in men in the 40-49 age group in the group  $\leq 85$  and 94% in the group  $\geq 120$  mm Hg diastolic. Roughly the same conditions are to be found on classification by systolic pressure. The findings in women are as pronounced as in men.

Marked accentuation of the aortic sound does not occur in the blood pressure groups  $\leq 145$  mm systolic and  $\leq 85$  mm diastolic (except for one woman in the highest age group). The frequency increases markedly with increasing blood pressure. The increase with age however shows a tendency to fall off with higher blood pressures (compare the blood pres-

Table 7.24 *Accentuation of the second aortic heart sound*

Number of individuals with slight (+) and marked (++) accentuation compared to number of individuals in the different age and blood pressure groups (No.)

| Diastolic BP |     | Age groups |       |       |       |       |      | Total |          |
|--------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|              |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Females      |     |            |       |       |       |       |      |       |          |
| ≤ 85         | +   | 2          | 3     |       | 1     | 3     | 6    | 15    | 15       |
|              | ++  |            |       |       |       |       |      |       |          |
|              | No. | 13         | 31    | 19    | 19    | 11    | 10   | 109   |          |
| 90-100       | +   | 4          | 20    | 38    | 40    | 46    | 37   | 185   | 47.9     |
|              | ++  |            |       | 5     | 8     | 10    | 11   | 34    |          |
|              | No. | 34         | 53    | 9     | 86    | 71    | 57   | 396   |          |
| 105-115      | +   | 1          | 11    | 24    | 24    | 23    | 16   | 99    | 58.30    |
|              | ++  |            | 2     | 12    | 13    | 13    | 12   | 52    |          |
|              | No. | 1          | 16    | 44    | 40    | 40    | 30   | 171   |          |
| ≥ 120        | +   |            | 2     | 6     | 8     | 8     | 11   | 35    | 32.55    |
|              | ++  |            | 2     | 14    | 23    | 15    | 7    | 61    |          |
|              | No. |            | 4     | 5     | 36    | 26    | 20   | 110   |          |
| Total        | +   | 7          | 36    | 68    | 73    | 80    | 70   | 334   | 43.19    |
|              | ++  |            | 4     | 31    | 44    | 38    | 30   | 147   |          |
|              | No. | 48         | 104   | 183   | 180   | 148   | 117  | 780   |          |
| Males        |     |            |       |       |       |       |      |       |          |
| ≤ 85         | +   | 2          | 2     | 2     | 2     | 4     | 2    | 14    | 10       |
|              | ++  |            |       |       |       |       |      |       |          |
|              | No. | 48         | 33    | 16    | 15    | 12    | 10   | 134   |          |
| 90-100       | +   | 13         | 22    | 19    | 19    | 21    | 12   | 106   | 31.3     |
|              | ++  |            | 2     | 2     |       | 4     | 3    | 11    |          |
|              | No. | 88         | 76    | 61    | 46    | 50    | 21   | 345   |          |
| 105-115      | +   | 1          | 4     | 10    | 14    | 15    | 11   | 55    | 53.30    |
|              | ++  |            | 1     | 4     | 6     | 3     | 3    | 21    |          |
|              | No. | 6          | 8     | 22    | 23    | 23    | 21   | 103   |          |
| ≥ 120        | +   |            | 2     | 10    | 9     | 8     |      | 31    | 61.35    |
|              | ++  |            | 1     | 7     | 6     | 3     | 1    | 18    |          |
|              | No. |            | 3     | 18    | 16    | 11    | 3    | 51    |          |
| Total        | +   | 16         | 30    | 41    | 44    | 48    | 27   | 206   | 33.8     |
|              | ++  |            | 4     | 13    | 12    | 12    | 9    | 50    |          |
|              | No. | 142        | 120   | 120   | 100   | 96    | 53   | 633   |          |

Table 7-3. Accentuation of the second aortic heart sound

Number of individuals with slight (+) and marked (++) accentuation compared to number of individuals in the different age and blood pressure groups (No.)

| Systolic BP |     | Age groups |       |       |       |       |      | Total |          |
|-------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|             |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| F m a l     |     |            |       |       |       |       |      |       |          |
| ≤ 145       | +   | 2          | 4     | 2     | 4     | 6     | 5    | 23    | 16       |
|             | ++  |            |       |       |       |       |      |       |          |
|             | No. | 28         | 39    | 30    | 27    | 14    | 8    | 146   |          |
| 150-175     | +   | 5          | 24    | 43    | 34    | 25    | 15   | 146   | 49       |
|             | ++  |            | 1     | 4     | 7     | 5     | 3    | 20    |          |
|             | No. | 20         | 53    | 89    | 72    | 42    | 20   | 296   |          |
| 180-205     | +   |            | 8     | 18    | 28    | 37    | 33   | 124   | 62       |
|             | ++  |            | 2     | 9     | 15    | 15    | 14   | 53    |          |
|             | No. |            | 11    | 35    | 47    | 55    | 33   | 201   |          |
| ≥ 210       | +   |            |       | 4     | 7     | 12    | 17   | 40    | 29       |
|             | ++  |            | 1     | 18    | 22    | 18    | 14   | 73    |          |
|             | No. |            | 1     | 29    | 34    | 37    | 36   | 137   |          |
| Total       | +   | 7          | 36    | 67    | 73    | 80    | 70   | 330   | 43       |
|             | ++  |            | 4     | 31    | 44    | 36    | 31   | 146   |          |
|             | No. | 48         | 104   | 183   | 180   | 148   | 117  | 780   |          |
| M a l       |     |            |       |       |       |       |      |       |          |
| ≤ 145       | +   | 3          | 5     | 4     | 2     | 4     | 4    | 22    | 10       |
|             | ++  |            |       |       |       |       |      |       |          |
|             | No. | 63         | 34    | 38    | 27    | 18    | 8    | 210   |          |
| 150-175     | +   | 11         | 20    | 19    | 20    | 17    | 6    | 93    | 35       |
|             | ++  |            | 2     | 4     | 8     | 4     | 4    | 14    |          |
|             | No. | 71         | 56    | 48    | 36    | 38    | 18   | 267   |          |
| 180-205     | +   | 2          | 4     | 12    | 17    | 17    | 11   | 63    | 60       |
|             | ++  |            | 2     | 6     | 3     | 3     | 4    | 18    |          |
|             | No. | 6          | 9     | 31    | 24    | 24    | 21   | 105   |          |
| ≥ 210       | +   |            | 1     | 6     | 5     | 10    | 6    | 28    | 35       |
|             | ++  |            |       | 3     | 7     | 5     | 1    | 18    |          |
|             | No. |            | 1     | 13    | 13    | 16    | 8    | 51    |          |
| Total       | +   | 16         | 30    | 41    | 44    | 48    | 27   | 206   | 33       |
|             | ++  |            | 4     | 11    | 12    | 12    | 9    | 50    |          |
|             | No. | 142        | 120   | 170   | 100   | 96    | 55   | 633   |          |

sure group 180-203 mm systolic) Finally in the highest blood pressure group ( $\geq 210$  mm systolic) a fall is to be seen in the two highest age groups in both sexes. The

same tendency is to be seen in the group  $\geq 120$  mm diastolic.

A statistical analysis of these findings gives the following results

Table 7.2<sup>a</sup> Accentuation of second aortic sound

| Sex                        | Systolic  |          | Diastolic |           |
|----------------------------|-----------|----------|-----------|-----------|
|                            | BP        | Age      | BP        | Age       |
| All grades of accentuation |           |          |           |           |
| Females                    | (3) 98.6  | (3) 28.4 | ( ) 154.3 | (4) 29.1  |
| Males                      | (7) 91.1  | (3) 3.2  | (2) 245.1 | (2) 12.9* |
| Marked accentuation        |           |          |           |           |
| Females                    | (2) 114.1 | (3) 3.5  | (2) 92.4  | (3) 1.5   |
| Males                      | (2) 24.0* | (1) 1.2  | (2) 28.3  | (1) 0.0   |

### 1) All grades of accentuation

In both sexes the youngest age group has been excluded. In women the age groups 30-39 and 40-49 have been combined. When classified by systolic pressure a 4 times 4 grouping has been used. In the diastolic classification 3 blood pressure groups ( $\geq 100$  105-115 and  $\geq 120$ ) have been used keeping the age groups from 30-39 unaltered.

In men the 2 lowest blood pressure groups are combined and further the age groups 30-39 and 40-49 are grouped together in both classifications. When classified by diastolic pressure the two oldest age groups are also combined.

The  $\chi^2$  test shows a highly significant difference between the blood pressure groups, pointing to an influence of blood pressure. The influence of age is also statistically significant in both sexes, except in men classified by systolic pressure.

### 2) Marked accentuation

In both sexes 3 blood pressure groups (the two lowest combined) have been used in both classifications. In women classified by systolic pressure the age groups 30-39 and 40-49 have been combined in the diastolic classification the 2 youngest age groups are omitted. In men this sign

occurs infrequently therefore only two age groups have been used (30-59 and 60 or higher)

The results of the  $\chi^2$  test show a significant difference between the blood pressure groups in both sexes in both classifications. However no significant difference between the age groups is to be seen in either sex.

### The influence of the lability of the blood pressure

On analysing the series in the blood pressure group  $\geq 105$  mm Hg by the method given on page 153 one finds that in women there is no essential difference in the total frequency of slight accentuation of the aortic sound between the non-labile (90%) and the labile groups (87%). On the other hand, there is a considerable difference in the frequency of marked accentuation of the aortic sound. The total frequency is thus 54% and 37% in the respective groups. The difference is most marked in the younger age groups (30-49 years) see Table 7.27

The  $\chi^2$  test shows a significant difference between the two blood pressure groups ( $0.05 < P < 0.01$ ) but an insignificant difference between the age groups.

Table 7.27 *Marked accentuation of the second aortic heart sound in relation to blood pressure lability*  
 Number of individuals with marked accentuation (+) compared to number of individuals in the different age and blood pressure groups (No.)

| Diastolic BP  |            |     | Age groups |       |       |       |       |      | Total |          |
|---------------|------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|               |            |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| F e m a l e   |            |     |            |       |       |       |       |      |       |          |
| Sitting ≥ 105 |            | +   | 1          | 8     | 30    | 32    | 25    | 20   | 116   | 47       |
|               |            | No. | 2          | 24    | 68    | 59    | 32    | 45   | 250   |          |
| Resting       | Non-labile | +   | 1          | 6     | 24    | 18    | 16    | 12   | 77    | 54       |
|               |            | No. | 1          | 11    | 44    | 56    | 26    | 26   | 144   |          |
|               | Labile     | +   |            | 2     | 11    | 14    | 9     | 8    | 39    | 57       |
|               |            | No. | 1          | 13    | 24    | 23    | 26    | 19   | 106   |          |
| M a l e s     |            |     |            |       |       |       |       |      |       |          |
| Sitting ≥ 105 |            | +   |            | 2     | 8     | 11    | 6     | 6    | 33    | 28       |
|               |            | No. | 3          | 9     | 31    | 30    | 28    | 15   | 118   |          |
| Resting       | Non-labile | +   |            | 1     | 6     | 7     | 2     |      | 16    | 29       |
|               |            | No. | 2          | 4     | 14    | 15    | 15    | 6    | 56    |          |
|               | Labile     | +   |            | 1     | 2     | 4     | 4     | 6    | 17    | 27       |
|               |            | No. | 3          | 5     | 17    | 15    | 15    | 9    | 62    |          |

In the low blood pressure group ( $\leq 100$  mm Hg) there is a minimal or no difference between the labile and non-labile groups. Thus slight accentuation occurs in 44% and 48% and marked accentuation in 7.4% and 7.2% respectively.

In men (blood pressure group  $\geq 105$  mm Hg) no essential difference is to be found in the frequency of either slight or marked accentuation of the aortic sound in either of the two groups under consideration. The frequency of slight accentuation is recorded as 85% and 77% and marked accentuation as 29% and 27% in the non-labile and the labile blood pressure groups respectively.

The corresponding values for the groups with low blood pressure are 26% for slight, and 2.1% for marked accentuation in the non-labile groups, and 26% and 1.6% respectively in the labile.

### Summary

Second aortic sound, graded into slight and marked accentuation, is influenced by age and blood pressure in both sexes.

This is similar to the other cardiac findings.

Slight accentuation is markedly influenced by age in groups with low blood pressure in both sexes, while the frequency is about the same for all ages in groups with high blood pressure (Fig. 7.17).

Marked accentuation does not occur in groups with low pressures ( $\leq 145$  systolic and  $\leq 85$  diastolic) except for one woman in the highest age group. The frequency increases markedly with increasing blood pressure, but has a tendency to fall off with higher pressures in the two highest age groups.

$\chi^2$  test shows a highly significant difference between the blood pressure groups in both sexes with all grades and with marked accentuation. However no signi-



significant difference is found between the age groups with marked accentuation.

There is a significant difference between the non-labile and labile groups with marked accentuation in women, but not in men.

### Discussion

The physical evaluation of the size of the heart as well as the auscultatory findings show the same pattern indicating an influence of age and of blood pressure. It must be pointed out that the calculations have been based on the reduced series (see p. 121 and Table 7 I). The frequency of some of the findings (displacement of the apex and heaving apex beat) is quite different when the total series is considered.

As was expected the frequency of the different cardiac findings was very varied. Consequently the influence of blood pressure and of age judged statistically will give varied data. Some findings, such as a heaving apex beat and gallop rhythm, occur so rarely that they do not lend themselves to statistical study.

On evaluating the different findings separately one sees that with the technique used the apex beat cannot be localized as often in the higher age groups as in the younger (see Fig 7 II). This finding confirms those of Isaac & Levy (104) Mainland & Gordon (138) and Niehaus & Wright (163). This study shows that the influence of age is even and unrelated to the blood pressure grouping and the demonstrability of the apex beat decreases somewhat faster in men than in women. On an average the frequency of a palpable apex beat in this study among the young men and women with normal blood pressure (diastolic  $\leq 85$  mm) is markedly greater than in that of Niehaus & Wright. While the apex can be felt in 87% of the men in the 30-39 age group and in 81% of the women, Niehaus & Wright's findings are 27% and 37% respectively. In the other age groups the conditions are the same. The findings of Isaac & Levy

(104) and Eve (65) are more in accordance with the findings in this study.

The probable explanation of the decreasing demonstrability of the apex beat is increasing pulmonary emphysema and adiposity with advancing age, as well as the condition of the chest wall. No tests of pulmonary function have been carried out in this study; therefore the relationship between age and pulmonary emphysema and the palpable apex beat cannot be investigated further. A correlation between weight, age and the palpable apex beat, on the other hand, can be done easily. Niehaus & Wright found that with an increase of the body weight the demonstrability of the apex beat decreased rapidly, somewhat faster in the men than in the women. Their series, however, was only divided into groups by weight, without regard to age.

In spite of these influences, this series shows a considerable increase in the frequency of displacement of the apex beat with increasing age in addition to the increasing frequency with rising blood pressure. A classification into an apex beat up to 9 cm and a displaced one (10 cm or more from midsternal line) gives much the same results (see Fig 7 II). The statistical calculations, however, are based entirely on the displaced apex beats. The increase with rising blood pressure is marked. In the groups with high blood pressure ( $\geq 120$  mm diastolic) very few individuals are to be found with an apex beat  $\leq 8$  cm from the midline. This finding is more pronounced in men. Finally it appears that the frequency of a displaced apex beat in the two highest blood pressure groups (diastolic 105-115 and  $\geq 120$  mm Hg) shows a tendency to decrease in the highest age groups compared to the 50-59 age group in both sexes. This could be an indication of an influence of excess mortality (compare earlier remarks on the symptom angina pectoris, p. 154 and later on the heart size judged electrocardiographically and radiologically, pp. 192 and 215).

In the survey of the literature the findings of some authors regarding the physical evaluation of the size of the heart have been given. It is mainly in the earlier works that one finds this information while the more recent ones mainly discuss the size of the heart on the basis of the radiological and electrocardiographic findings. Very few of the authors referred to have paid particular attention to the age distribution of the series in their evaluation.

The *auscultatory* findings over the apex show similar tendencies with a higher frequency of systolic murmurs with increasing age and blood pressure. The frequency of the moderate systolic murmurs (Levine's grades 2-3 and 3) shows an even rate of increase from the lowest to the highest blood pressure group. In women the frequency increases from 21% to 45% classified by diastolic pressure and from 14% to 45% classified by systolic pressure. In men the corresponding figures are 13% and 22% on diastolic, and 10% to 31% on systolic classification of the series (see Tables 7.19 and 7.20). While the influence of age is marked in the groups with low blood pressure (see Fig. 7.15) the frequency in the groups with higher blood pressure is about the same in the younger age groups as in the older ones. The frequency of Levine's grades 3-4 or higher is, as would be expected, very low and one can hardly draw conclusions from the data. The sex difference illustrated in Fig. 7.15 is probably due to the heavier musculature and chest wall in men decreasing the intensity of the murmur.

One should be careful when making comparisons with the findings of other authors but the frequency of apical systolic murmurs is not unlike that given by P. Ullin, Bowcock & Wood (171) or by Mathisen (144) when the blood pressure group of  $\geq 105$  mm diastolic is used as the basis for comparison. Paulin, Bowcock & Wood found mitral systolic murmurs in 26%. Mathisen found them in 33.8% without any significant sex difference

while this series shows an average frequency of 25% in men and 49% in women. Otherwise there are very few studies based on ambulant patients in which these heart findings have been studied.

The systolic murmurs over the *base of the heart* show the same pattern, indicating an effect of blood pressure and of age in both sexes, most marked in women (see the statistical findings, p. 169).

The sex difference is marked. The frequency of all grades of aortic murmurs in women with a diastolic blood pressure of  $\geq 105$  mm is on an average 53% and in men it is 26%. The frequency of loud and very loud murmurs in the same blood pressure groups is on an average 25% in women and 8% in men. The sex difference must be assumed to be due to the anatomical features mentioned above.

Most of the authors (see p. 162) think that the systolic murmurs are due to an aortic dilatation, in other words, to an extra cardiac condition (Müller 161). On the other hand, the frequency of very loud systolic murmurs of a stenotic type in the highest age groups can also point to arteriosclerotic valve changes playing their part. Even though these stenotic murmurs occur almost entirely in the highest age groups in both sexes, and even though all rheumatic and other types of valve lesion have been eliminated as far as possible from this study this does not exclude the possibility that cases with rheumatic valve lesions can occur in these age groups. Their predominant occurrence in the highest blood pressure groups in both sexes indicates a connection with hypertension. This is in agreement with Fahberg, who holds that hypertension is undoubtedly of great importance in the production of valvular lesions, much as it favours the occurrence of arteriosclerosis of the vessel.

*Diastolic murmurs resulting from functional aortic insufficiency* were found in very few cases that is in 3 women in the 50-59 age group, and in one man in the 40 and one in the 60 age group all with

a diastolic blood pressure of  $\geq 120$  mm Hg. In none of these patients could signs or symptoms of rheumatic or syphilitic heart disease be found. (The occurrence of hypertension in combination with valve lesions of the heart will not be touched on in this monograph.) For comparison it can be mentioned that Paullin Bowcock & Wood (238) found aortic systolic murmurs in 5% and aortic diastolic murmurs in 2%. Mathisen (141) found diastolic murmurs in 31%.

Accentuation of the *second aortic sound* is the clinical cardiac finding that shows the most marked increase in frequency with age and blood pressure in both sexes and according to both blood pressure classifications. The markedly accentuated (rough or ringing) aortic sound does not occur in the blood pressure groups  $\leq 145$  mm systolic or  $\leq 85$  mm diastolic (with the exception of one woman in the  $\geq 70$  age group) but the increase in frequency with rising blood pressure is prominent in both sexes. There is little sex difference in the frequency of the slighter degrees of accentuation; on the other hand, the frequency of marked accentuation is essentially commoner in women (compare Fig. 7.17). This sex difference is perhaps dependent on the anatomical conditions mentioned before.

In common with the other physical cardiac findings a fall in the frequency is to be seen in the 2 highest age groups in both sexes, whether the series is classified by systolic or diastolic blood pressure. The possibility of an excess mortality effect has been suggested earlier (see page 178).

Comparison with the data of other authors is difficult, as the grading is highly subjective. Janeway (105) states the frequency for men and women together. Thus the average frequency of moderate and marked accentuation in the deceased group (moderate 46% marked 17%) is considerably higher than the corresponding figures in the survivors (39% and 6% respectively). Mathisen (141) found accentuation in 23.5% with the same fre-

quency in men and women at the time of the first investigation. The average figures for the whole of the present series, regardless of the blood pressure grouping, give findings that are not unlike those referred to above, being for women slight accentuation 43% and marked 19% and for men 33% and 8% respectively. When the series is divided into groups, the frequency is essentially higher in the higher blood pressure groups, particularly for women.

The explanation of the accentuation seems to be the pressure increase in the systemic circulation. But accentuation of the aortic sound does not occur only in hypertension. In aortitis and arteriosclerosis with consequent elongation of the aorta, which is thus more closely approximated to the chest wall, all degrees of accentuation of the aortic sound occur according to Fishberg (69). The loss of elasticity and stiffness in the wall and valve cusps can give the second aortic sound a clanging metallic quality described by Müller as an exhaust pipe sound.

The blood pressure effect which the accentuated aortic sound shows in this series is therefore not only an expression of the increased aortic pressure but may also be explained by increasing sclerosis and calcification of the aorta and aortic cusps. To what extent the sclerosis of the aorta develops to a greater degree in individuals with high blood pressure than in those with lower blood pressure cannot be judged from these auscultatory findings.

The physical cardiac findings have also been investigated in relation to the lability of the blood pressure. On the whole there is a slight tendency to a greater frequency of some pathological cardiac findings in the non-labile group. But the findings are not always the same in the two sexes, and the statistical analyses do not show any significant difference between the blood pressure groups, except for marked accentuation of the aortic sound.

### III The electrocardiographic findings

#### *Survey of the literature*

The electrocardiographic technique has been considered to be one of the best and most sensitive methods of estimating the size of the heart. Our present knowledge is based on the correlation between the electrocardiographic findings and clinical and post-mortem observations. However few electrocardiographic problems can be solved on an entirely empirical basis. The electrocardiographic findings are based on a large number of experimental investigations, dictated by well-founded hypotheses. In spite of this there are still several objections to the criteria commonly used in the estimation of cardiac hypertrophy.

It has been known for a long time that hypertrophy of the chambers of the heart gives characteristic electrocardiographic changes in the standard leads. This was recognised by Einthoven and his co-workers (59). In 1911 Lanetaky (131) described the influence of age, blood pressure, and the size of the heart on the electrocardiogram. Further studies by the London school (T. Lewis) and the Vienna school (Wenckebach and others) clarified certain features of the electrocardiogram in hypertrophy but in the first decades interest was primarily centred on the arrhythmias and myocardial diseases.

The criteria of left ventricular hypertrophy that are now used are based in the main on new work. Nearly all compare the electrocardiographic findings with clinical data, while few are based on autopsy findings.

In 1930 Master (141) gave left axis deviation as the most common finding (74%) among 152 hypertensive patients, with a blood pressure habitually above 160 mm systolic and 90 mm diastolic. Left axis deviation combined with  $T_i$  inversion occurred in 30% while left axis deviation combined with high voltage and depression of the  $ST_i$  segment was rare. Master found that these electrocardiographic

changes took place gradually depending on the duration of the hypertension and the degree of enlargement of the left ventricle, and not on changes in the heart muscle.

Rykert & Hepburn (200) examined the electrocardiograms of the so-called coronary type characterised by depression of  $ST_i$  and inversion of  $T_i$  together with elevation of  $ST_{III}$  combined with left axis deviation. A closer clinical investigation and follow-up study of 143 patients including post mortem examination made it clear that hypertension and lesions of the aortic valve were the most common cause of illness. They concluded that these distinctive electrocardiographic abnormalities were characteristic of certain cases of left ventricular hypertrophy and since arterial hypertension was by far the most frequent determining cause of that hypertrophy that these electrocardiographic changes were practically diagnostic of hypertension.

Others have verified the common occurrence of left axis deviation in hypertension. Thus Schloemka (202) in a series of 500 individuals of all ages who had neither heart nor circulatory disease found that left axis deviation, calculated according to the Type index increased with age. The author considered this to be a normal age change. Among 367 hypertensives left axis deviation was to be found even more frequently than would be expected at their age. Similarly, van Nieuwenhuizen & Hartog (228) found the same tendency among 228 hypertensives.

Gubner & Ungerleider (87) found that it was necessary to establish specific criteria for left ventricular hypertrophy in connection with a prognostic study on hypertension. The electrocardiogram was analysed in 3 groups of individuals: 1) Normal individuals (460 applicants for life insurance) with left axis deviation in whom the blood pressure had always been recorded as under 140 mm systolic and 90 mm diastolic, and who were without cardiac symptoms. 2) A mixed group,

a diastolic blood pressure of  $\geq 120$  mm Hg. In none of these patients could signs or symptoms of rheumatic or syphilitic heart disease be found. (The occurrence of hypertension in combination with valve lesions of the heart will not be touched on in this monograph.) For comparison it can be mentioned that Paulin, Bowcock & Wood (238) found aortic systolic murmurs in 6 and aortic diastolic murmurs in 2. Mathisen (144) found diastolic murmurs in 31.

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ance must be placed on the precordial leads for electrocardiographic diagnosis.

Further many workers, among others Schach, Rosenman & Katz (201) and Goulder & Kassane (81) have worked on the electrocardiographic findings on application of unipolar limb leads. These criteria will not be discussed further as this method of registration has not been used in this work.

Studies of the autopsy findings and the heart weight correlated with the electrocardiographic criteria for left ventricular hypertrophy are, as has been mentioned, few but had already been carried out by Lewis (127) in 1914 and by Hermann & Wilson (96) in 1922.

Noth Myers & Klein (165) analysed Wilson's precordial leads in 84 pathologico-anatomically verified cases of left ventricular hypertrophy without myocardial infarction or appreciable gross fibrosis. The control series consisted of 32 cases in which the hearts were found to be normal at autopsy together with a second group of 50 young men with normal hearts by physical and roentgen examination. On comparison with the control series there was found to be no difference when judgment was based on the amplitude of the R waves in I and I' alone. On the other hand, there was a general trend toward increasing duration of Q R or R with increasing cardiac weight, but many individual exceptions were encountered.

Scott, Seiwert, Simon & McGuire (205) in an autopsy series of 100 cases of pure left ventricular hypertrophy have checked the reliability of the electrocardiographic criteria and investigated which of the present sets of diagnostic criteria give the greatest accuracy when compared with the autopsy findings. The thickness of the wall of the left ventricle was correlated to the generally accepted criteria put forward by the various authors. Gubner & Ungersfelder (87) criteria for the standard leads gave an accuracy of 36. Katz's (111) criteria

gave 40 % while if the criteria for the chest leads were added the accuracy increased to 59 %. One or more of Wilson and co-workers (236) criteria for the unipolar precordial leads gave an accuracy of 81 %. Sokolow & Lyon's (218) criteria for the precordial leads gave 75 % accuracy the unipolar limb leads 47 % and the combination 85 %. Finally the accuracy of Noth and co-workers (165) criteria was 28 %. The accuracy of the unipolar limb leads was less than for the unipolar precordial leads, but was greater than that of the standard leads.

Selzer, Ebnother Packard, Stone & Quinn (207) have recently studied 108 tracings of the left ventricular hypertrophy pattern. An analysis of the necropsy findings based on heart weights revealed that left ventricular hypertrophy was believed to be present in 75 cases, absent in 17 cases, and questionable in 16 cases. They evaluated the frequency of the 3 main changes of electrocardiographic criteria: high voltage, prolonged ventricular activation time, and ST-T alterations. In the 75 cases of hypertrophy proved at autopsy these criteria were seen in 71, 40, and 63 cases respectively. In the 17 cases with normal heart weights there was a false diagnosis of hypertrophy. While high voltage in the precordial leads was the most sensitive sign in the cases of hypertrophy it was also most frequently responsible for the false diagnosis of hypertrophy.

Recently Allenstein & Mon (5) evaluated the electrocardiographic diagnosis of ventricular hypertrophy based on autopsy comparison the thickness of the ventricular wall was used as the indication of hypertrophy. Sixty-five cases were examined of whom 32 had anatomically normal hearts, 17 had isolated left ventricular hypertrophy while 16 had isolated right ventricular hypertrophy. The criteria of Wilson and co-workers, and Sokolow & Lyon, showed relatively high positives, but they also had a high frequency of false positives. The reason for this was

a clock-wise rotation of the heart along its longitudinal axis.

In this survey of the literature, those studies that describe the different electrocardiographic signs of left ventricular hypertrophy have been referred to first and foremost as they have formed the basis for the evaluation of the criteria in this work. The studies that deal only with the frequency of pathological electrocardiographic findings in hypertension have not been included here.

One also finds summaries of these criteria of left ventricular hypertrophy in the more recent textbooks on heart diseases and hypertensive illness and in the electrocardiographic literature. Reference is therefore made to Friedberg (76) Flahberg (69) together with Lipman & Mandle (132) Stroud & Stroud (224) and Wood (238).

Study of the literature shows that our knowledge of the hypertensive electrocardiographic pattern is mainly empirical. The studies are mainly based on series that fall into 3 categories: groups with hypertension and verified left ventricular hypertrophy; groups with hypertension and presumed left ventricular hypertrophy; together with control series of individuals free from disease of the heart or circulatory system. Most of the hypertensive series are ill defined as regards the degree, type, and duration of the hypertension.

In the pathologico-anatomical studies the electrocardiographic patterns of left ventricular hypertrophy have been correlated to the anatomical findings. In these studies it appears that the criteria based on the unipolar precordial leads are the most reliable. It must be stressed that several authors have suggested that a possible source of misinterpretation may lie in the fact that left ventricular hypertrophy can occur in the absence of noticeable electrocardiographic changes. There are, however, few studies showing the occurrence of false positive electrocardiograms.

Thus the criteria available at present for the diagnosis of left ventricular hyper-

trophy appear to be moderately satisfactory. According to Selzer and co-workers (207) it is necessary to accept them as an expression of probability rather than a diagnosis of left ventricular hypertrophy.

### Definition

In accordance with the studies in the literature we have chosen to base the diagnosis of left ventricular hypertrophy on the following criteria:

1) High amplitude in the *QRS* complex in the precordial leads with a low or absent *R* in *I* and *I<sub>1</sub>* and high *R* in *I* *I<sub>1</sub>* combined with a deep *S* in *I*.

2) The changes in the *ST-T* segment and the *T* wave over the left ventricle, with depression of *ST* and flattening or inversion of *T* in *I<sub>1</sub>*, *I<sub>2</sub>*. Further a depression of the *ST* line of 0.5 mm or more in lead *I* combined with left axis deviation, and in the same way a flattened *T* (less than 1 mm) combined with left axis deviation.

3) Increased duration of the *QRS* complex to 0.12 sec. without signs of left bundle branch block. Further delayed activation time of the left ventricle measured from the beginning of *QRS* to the peak of the *R* wave in *I* or *I<sub>1</sub>* (intrinsic deflection 0.06 sec. or more).

It must be pointed out that the diagnosis of left ventricular hypertrophy was not based exclusively on a single one of these criteria. The judgment was made after an evaluation and correlation of all the abnormal tendencies in the different leads. Left axis deviation alone without other signs is not considered a sign of hypertrophy but it has been recorded as a separate finding in the arrangement of the material. Next, the cases with left axis deviation in which the *QRS* complex in the standard leads shows a high amplitude have not been included, in accordance with the views of Gubner & Ungerleider (87). According to Lipman and Mandle, this is only correct in the cases in which the hypertrophied heart is in a horizontal position (judged by the unipolar limb leads).

### Method and apparatus

The electrocardiogram was recorded on all individuals with 3 bipolar limb or standard leads, together with 6 unipolar precordial leads (V 1<sub>6</sub>) in the conventional precordial positions. The unipolar limb leads were not used systematically and are not included in this study.

The apparatus used was the Elema Electrocardiograph Klinikk type Em 130 with 4 channels.

All electrocardiographic tracings of the different deflections, segments, and levels have been measured in detail for further studies. However to get a survey of the main groups of the electrocardiographic changes the following subdivisions have been used

- 1 ECG not registered or technical failure which makes judgment impossible.
- (0) 2. No pathological findings.
- (1) 3. Isolated left axis deviation.
- (2) 4. Left ventricular hypertrophy retardation
- (3) 5. Left bundle branch block.
- (4) 6. Fibrillation or flutter combined with left ventricular hypertrophy
- (5) 7. Right axis deviation and right ventricular hypertrophy
- (6) 8. Myocardial infarction.
- (7) 9. Rhythm disturbances except 4-8 (2-6) findings.
- (8) 10. Functional changes (digitalis etc.)
- (9) 11. Special findings (WPFH syndrome, Wilson type low voltage etc.)

The number given in parentheses refers to the codes on the punch cards.

### Personal findings

In this monograph a survey will be given of the left ventricular hypertrophy pattern, code No. 2) and of isolated left axis deviation code No. (1) The code numbers (3) and (4) are also included in the pattern of left ventricular hypertrophy

Electrocardiograms not registered or technically erroneous were very few 6 out of total 1,550 (0.4%). Left bundle

branch block was also rare 4 electrocardiograms among 633 men (reduced series) (0.6%) and 3 electrocardiograms among 780 women (0.4%). There was no clear tendency for these changes to occur in the highest blood pressure groups but divided according to age all cases, except for one woman, occurred above 60 years of age. Fibrillation or flutter combined with left ventricular hypertrophy occurred in 3 cases among the men and in 1 case among the women.

Judged on the basis of the criteria given above, the reduced series (Tables 7.1 subgroup 2) shows an increase in the frequency of left ventricular hypertrophy with rising blood pressure in both sexes. Further in each of the blood pressure groups a considerable increase is to be seen with age. This is apparent from Table 7.28 when the series is classified by diastolic pressure and from Table 7.29 for the systolic classification in the same way the influence of age and blood pressure are illustrated in Figures 7.18 and 7.19 page 188.

According to the diastolic pressure classification sporadic cases of left ventricular hypertrophy are to be seen in the blood pressure group  $\leq 85$  mm, for instance in one woman in the 50-59 age group, and in one man in the youngest, and 5 in the two oldest age groups. A considerable increase in the prevalence is to be seen with increasing blood pressure in all the age groups. In the blood pressure group  $\geq 120$  mm signs of left ventricular hypertrophy occur in 50-60% of men and women over 40 years of age.

When the series is classified by systolic pressure the influence of age and of blood pressure are seen to be similar. In the blood pressure group  $\geq 210$  mm left ventricular hypertrophy is to be found in 50-60% of the women in the age groups over 40 years. In men the highest prevalence is to be seen in the 50-59 age group (69%) after this the prevalence decreases in the two highest age groups.

If one considers the frequency of left axis



Table 7.28. *Electrocardiographic signs of left ventricular hypertrophy*

Number of individuals with left ventricular hypertrophy (+) compared to number of individuals in the different age and blood pressure groups (No.)

| Diastolic BP |                 | Age groups |       |       |       |       |      | Total |          |
|--------------|-----------------|------------|-------|-------|-------|-------|------|-------|----------|
|              |                 | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Females      |                 |            |       |       |       |       |      |       |          |
| ≤ 85         | $\frac{+}{No.}$ | 13         | 31    | 19    | 19    | 11    | 10   | 103   | 1        |
| 90-100       | $\frac{+}{No.}$ | 34         | 2     | 2     | 9     | 12    | 21   | 46    | 12       |
| 105-115      | $\frac{+}{No.}$ | 1          | 3     | 7     | 13    | 12    | 12   | 47    | 28       |
| ≥ 120        | $\frac{+}{No.}$ |            |       | 12    | 20    | 15    | 12   | 59    | 54       |
| Total        | $\frac{+}{No.}$ | 48         | 3     | 21    | 43    | 39    | 43   | 153   | 20       |
| Males        |                 |            |       |       |       |       |      |       |          |
| ≤ 85         | $\frac{+}{No.}$ | 2          | 33    | 16    | 15    | 2     | 3    | 7     | 5        |
| 90-100       | $\frac{+}{No.}$ | 88         | 3     | 1     | 2     | 5     | 3    | 14    | 4        |
| 105-115      | $\frac{+}{No.}$ | 6          | 8     | 4     | 7     | 5     | 10   | 26    | 5        |
| ≥ 120        | $\frac{+}{No.}$ |            | 1     | 9     | 10    | 7     |      | 29    | 57       |
| Total        | $\frac{+}{No.}$ | 2          | 4     | 14    | 19    | 19    | 18   | 76    | 12       |

deviation one sees that in women there is a marked increase with increasing age in the two lowest blood pressure groups (≤ 85 mm diastolic and ≤ 145 mm systolic). This influence of age is not so obvious in the men, and is to be seen only when the series is classified by systolic pressure. Next, it is seen among the women that the frequency of left axis deviation decreases with higher blood pressure. Further in the two

highest blood pressure groups (≥ 210 mm systolic and ≥ 120 mm diastolic) the frequency of left axis deviation decreases with increasing age. While the frequency in the 40-49 age group with a blood pressure ≥ 120 mm diastolic is 40%, the frequency in the age group ≥ 70 years is only 15%. The corresponding figures in the blood pressure group ≥ 210 mm systolic are 33% and 19%.

Table 7.29 Electrocardiographic signs of left ventricular hypertrophy

Number of individuals with left ventricular hypertrophy (+) compared to number of individuals in the different age and blood pressure groups (No.)

| Systolic<br>BP |          | Age groups |       |       |       |       |      | Total |             |
|----------------|----------|------------|-------|-------|-------|-------|------|-------|-------------|
|                |          | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per<br>cent |
| Females        |          |            |       |       |       |       |      |       |             |
| ≤ 145          | +<br>No. | 28         | 39    | 30    | 27    | 14    | 8    | 146   | 0.7         |
| 150-175        | +<br>No. | 20         | 2     | 2     | 7     | 6     | 5    | 22    | 7           |
| 180-205        | +<br>No. |            | 3     | 5     | 16    | 11    | 18   | 53    | 26          |
| ≥ 210          | +<br>No. |            | 11    | 35    | 47    | 35    | 53   | 201   |             |
|                |          |            |       | 14    | 19    | 22    | 22   | 77    | 57          |
|                |          |            | 1     | 29    | 34    | 37    | 36   | 135   |             |
| Total          | +<br>No. | 48         | 5     | 21    | 43    | 39    | 45   | 153   | 29          |
|                |          |            | 104   | 183   | 180   | 148   | 117  | 780   |             |

| Males   |          |          |          |           |           |          |          |           |     |
|---------|----------|----------|----------|-----------|-----------|----------|----------|-----------|-----|
| ≤ 145   | +<br>No. | 65       | 1<br>34  | 38        | 27        | 2<br>18  | 2<br>8   | 5<br>210  | 2.4 |
| 150-175 | +<br>No. | 1<br>71  | 2<br>56  | 4<br>48   | 2<br>36   | 6<br>38  | 5<br>18  | 20<br>267 | 3   |
| 180-205 | +<br>No. | 1<br>6   | 1<br>9   | 4<br>21   | 8<br>24   | 3<br>24  | 9<br>21  | 26<br>103 | 25  |
| ≥ 210   | +<br>No. |          |          | 6<br>13   | 9<br>13   | 8<br>16  | 2<br>8   | 25<br>51  | 49  |
| Total   | +<br>No. | 2<br>142 | 4<br>120 | 14<br>120 | 19<br>100 | 19<br>96 | 18<br>53 | 76<br>633 | 12  |

The statistical analysis of left ventricular hypertrophy gives the following results

In both sexes the youngest age group (15-29 years) is excluded. In women 5 blood pressure groups (the two lowest combined into one) and 4 age groups (30-49, 50-59, 60-69 and 70 or higher) have been used in both classifications.

In men on diastolic classification a 3 times 2 grouping (age groups 30-39 and 60 or

higher) has been used. On systolic classification only 2 blood pressure groups (≤ 175, ≥ 180) and 3 age groups (30-49, 50-59, and 70 or higher) have been used, see Table 7.30.

The  $\chi^2$  test shows a significant difference between the blood pressure groups in both sexes in the two classifications. There is also a significant difference between the age groups except in men on diastolic classification ( $0.10 < P < 0.05$ ).



Table 7.30 *Electrocardiographic signs of left ventricular hypertrophy*

| Blood pressure |            | Age groups      |                  |                 |                 | $\chi^2$ test |
|----------------|------------|-----------------|------------------|-----------------|-----------------|---------------|
|                |            | 30-49           | 50-59            | 60-69           | $\geq 70$       |               |
| Female         |            |                 |                  |                 |                 |               |
| Diastolic      | $\leq 100$ | $\frac{4}{198}$ | $\frac{10}{103}$ | $\frac{12}{82}$ | $\frac{21}{67}$ | BP (2) 68.1   |
|                | 105-115    | $\frac{10}{60}$ | $\frac{13}{40}$  | $\frac{12}{40}$ | $\frac{13}{30}$ | Age (3) 17.0* |
|                | $\geq 120$ | $\frac{12}{29}$ | $\frac{20}{35}$  | $\frac{15}{26}$ | $\frac{12}{20}$ |               |
| Systolic       | $\leq 175$ | $\frac{4}{211}$ | $\frac{8}{99}$   | $\frac{6}{56}$  | $\frac{5}{28}$  | BP (2) 97.0*  |
|                | 180-205    | $\frac{8}{46}$  | $\frac{16}{47}$  | $\frac{11}{53}$ | $\frac{18}{53}$ | Age (3) 8.8*  |
|                | $\geq 210$ | $\frac{14}{90}$ | $\frac{19}{54}$  | $\frac{22}{57}$ | $\frac{22}{36}$ |               |

| Diast. BP | 30-59 | $\geq 60$ | $\chi^2$ test |
|-----------|-------|-----------|---------------|
|-----------|-------|-----------|---------------|

## M I

|            |                 |                 |             |
|------------|-----------------|-----------------|-------------|
| $\leq 100$ | $\frac{6}{230}$ | $\frac{13}{93}$ | BP (2) 53.8 |
| 105-115    | $\frac{11}{58}$ | $\frac{15}{44}$ |             |
| $\geq 120$ | $\frac{20}{37}$ | $\frac{9}{14}$  | Age (1) 3.6 |

| Syst. BP   | 30-49           | 50-69            | $\geq 70$       | $\chi^2$ test |
|------------|-----------------|------------------|-----------------|---------------|
| $\leq 175$ | $\frac{7}{196}$ | $\frac{10}{108}$ | $\frac{7}{26}$  | BP (1) 14.8*  |
| $\geq 180$ | $\frac{11}{44}$ | $\frac{28}{57}$  | $\frac{11}{29}$ | Age (2) 7.7*  |

*The influence of the lability of the blood pressure*

The frequency of left ventricular hypertrophy in the labile and non-labile groups has been calculated in the same way as for the previous cardiac findings (see page

133). The data are given in Table 7.31 and Figure 7.20.

The frequency in the non-labile groups is, on the whole, somewhat greater than in the labile. The difference is greatest in men in the 3 highest age groups, while in

Table 7.31 Left ventricular hypertrophy in relation to blood pressure lability

Number of individuals with left ventricular hypertrophy (+) compared to numbers of individuals in the different age and blood pressure groups (No.)

| Diastolic BP  |            |     | Age groups |       |       |       |       |      | Total |          |
|---------------|------------|-----|------------|-------|-------|-------|-------|------|-------|----------|
|               |            |     | 15-29      | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 70 | No.   | Per cent |
| Females       |            |     |            |       |       |       |       |      |       |          |
| Sitting ≥ 105 |            | +   | 2          | 4     | 21    | 27    | 21    | 23   | 96    | 39       |
|               |            | No. |            | 24    | 66    | 59    | 32    | 45   | 248   |          |
| Resting       | Non-labile | +   | 1          | 2     | 16    | 18    | 11    | 14   | 61    | 43       |
|               |            | No. |            | 11    | 42    | 36    | 26    | 26   | 142   |          |
|               | Labile     | +   | 1          | 2     | 5     | 9     | 10    | 9    | 33    | 33       |
|               |            | No. |            | 13    | 24    | 21    | 26    | 19   | 106   |          |
| Males         |            |     |            |       |       |       |       |      |       |          |
| Sitting ≥ 105 |            | +   | 5          | 1     | 10    | 13    | 9     | 7    | 42    | 36       |
|               |            | No. |            | 9     | 31    | 30    | 28    | 15   | 118   |          |
| Resting       | Non-labile | +   | 2          | 4     | 4     | 9     | 6     | 4    | 23    | 41       |
|               |            | No. |            | 4     | 14    | 15    | 15    | 6    | 56    |          |
|               | Labile     | +   | 3          | 1     | 6     | 6     | 3     | 3    | 19    | 31       |
|               |            | No. |            | 5     | 17    | 15    | 13    | 9    | 62    |          |

the women the greatest difference is to be seen in the younger age groups.

In women 4 age groups (30-49 50-59 60-69 and 70 or higher) and in men 2 age groups (40-59 and 60 or higher) have been used in the analyses.

The  $\chi^2$  test does not show any significant difference between the blood pressure groups in either sex. In women a significant difference between the age groups is seen ( $0.05 < P < 0.01$ )

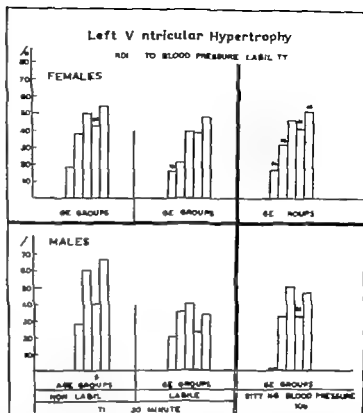
#### Discussion

In this study the electrocardiographic findings of isolated left axis deviation and those pointing to left ventricular hypertrophy with the use of the conventional electrocardiographic criteria are included but not typical changes of myocardial infarction, arrhythmias, and functional changes. It should be mentioned that the few electrocardiograms showing left bundle branch blocks have been included in the

hypertrophy findings, as most authors consider this finding as a sign of hypertrophy with or without dilatation when myocardial infarction is excluded. However it should be stressed that left bundle branch block is not always considered as a sign of left ventricular hypertrophy but as a sign of combined hypertrophy. These electrocardiographic changes occurred so rarely (0.5%) in the reduced series that the statistical analysis would hardly be influenced if these cases were excluded.

The frequency of the electrocardiographic criteria of left ventricular hypertrophy shows in all the same pattern as that disclosed by the clinical evaluation of the heart size. Statistical analysis has revealed a significant difference in the frequency between the blood pressure groups when the material is grouped according to the principles given. This difference between blood pressure groups is seen both when the material is classified by systolic and by diastolic pressure.

Fig 7.20. The figure shows the tendency to increase in the frequency of left ventricular hypertrophy in the non-labile blood pressure groups.



Studies of the literature show that this relationship of electrocardiogram to blood pressure is not to be verified in all series. Thus Rasmussen & Thimstad (188) in their selective hospital series including 69 women and 31 men with a mean age of 60 years, found that the actual height of the blood pressure had apparently no influence on the pathological electrocardiographic findings. The height of the blood pressure represented the stable pressure found by repeated examinations, the patients being kept in bed and under hospital regime. Evans, Mathews & White (64) did not find any definite positive correlation between the diastolic blood pressure on admission to hospital and the electrocardiographic alterations in the limb leads of their series (see p. 182). But in the precordial leads  $CF_1$ ,  $CF_2$  and  $CF_3$  the percentage of abnormal precordial

leads was greater in groups which had the highest blood pressure. Thus the total abnormal findings were 43 in the group 91-120/57 in the group 121-140 and 78 in the group with diastolic blood pressure over 140 mm Hg.

Similar findings are demonstrated by Leishman (119) who investigated a series of 218 hypertensive patients from a group whose progress was being observed at a special clinic, all below 60 years of age, and all with diastolic blood pressure of 100 mm Hg or more. He found that a considerably higher proportion of patients with abnormal than with normal electrocardiograms had severe diastolic hypertension. At the same time it was clear that severe hypertension was compatible with maintenance of a normal electrocardiogram.

Simpson (210) found that the frequency

of electrocardiographic changes was significantly related to the level of the average resting diastolic blood pressure. His series consisted of 203 hypertensive patients admitted to hospital. Eighty per cent of the patients were between 40 and 59 years of age. The patients were excluded from the study if their average diastolic blood pressure at rest in bed fell below 100 mm Hg. Subdivisions of the patients showed that the frequency of each type of electrocardiographic abnormality (high voltage, S-T depression, and T-wave changes) increased with rise in the diastolic blood pressure. T wave inversion was the most common criterion and occurred in women in 44 % in the group with diastolic blood pressure 100-109. The frequency increased steadily for each 10 mm group to 86 % in the group 140 mm and over. In men the values increased from 47 % to 91 % in the same blood pressure group. When comparing these figures with my own findings an increase in the prevalence of left ventricular hypertrophy is seen in the 40-59 age group in women from 6 % (diastolic blood pressure 90-100) and 24 % (105-115) to 53 % in the group 120 mm Hg or more, while the corresponding values in men are 3 %, 25 %, and 51 % respectively. However these data are based upon blood pressure measurement during the out patient examination (see p. 46) while Simpson's data represent average diastolic blood pressure at rest in bed.

The influence of the lability of the blood pressure upon the electrocardiographic signs of hypertrophy is not significant. The electrocardiographic changes, however are of higher frequency among the non-labile (stable) groups in both sexes. It was also shown that displaced apex beat, demonstrated by physical examination (see p. 160) was higher among the non-labile groups. Despite the fact that these methods of estimating the heart size are rather crude, both show a tendency towards a higher prevalence among the non-labile groups. Further studies are

necessary before any final conclusions can be drawn.

My findings have further shown a significant influence of age on the prevalence of the left ventricular hypertrophy electrocardiograms in both sexes in both classifications, except for men classified by diastolic pressure. This influence of age can be clearly seen from Figs. 7 18 and 7 19 within each blood pressure group.

Similar findings are seldom seen in previous papers on hypertension. Lelshman (119) explains that in his series older patients have not appeared especially liable to develop abnormal electrocardiograms. But Simpson, in his series, states that T-wave changes become more common as age advances.

There is in all very little difference in the frequency of left ventricular hypertrophy between the two sexes. The increase with age within the two sexes is nearly the same, but some minor differences might be emphasized. In the highest blood pressure group among the men, classified by systolic pressure, a decrease in the frequency of left ventricular hypertrophy is seen after the age of 50-59 years, while in the women a slight but steady increase is seen. Similar findings have been shown earlier (p. 178) and it has been suggested that it might be an effect of excess mortality within these groups. However this difference in the frequency of left ventricular hypertrophy between the two sexes is not seen in diastolic classification of the series, and the difference may well be due to differences in the attendance rate among these age groups. Nevertheless, examination of the total frequency of left ventricular hypertrophy and of left axis deviation among the women reveals a slight decrease with higher age in this blood pressure group. These slight differences, however can easily be ascribed to chance.

It is clear that the electrocardiographic changes are influenced by other factors, such as coronary disease and body weight. Persons with definite clinical and electro-

cardiographic signs of myocardial infarction have been excluded from this series, but the other cases with coronary disease remain. From the previous Tables (7 10 7 11 and 7 15) it can be seen that these cases make a total of 50 cases among the women and 29 cases among the men. If coronary heart disease (myocardial infarction excepted) was the cause of one or several of the criteria indicating left ventricular hypertrophy then the cases with angina pectoris would have shown a high incidence of such changes. According to Friedberg (76) and several others, the electrocardiograms are entirely normal in the large quantity of patients in whom there is no previous clinical history of myocardial infarction or heart failure. Neither did Simpson find any higher frequency of high voltage and T wave changes in his series in the patients with histories of angina of effort compared to the figures for the whole series. Therefore it is reasonable to suppose that the influence of coronary disease upon the major electrocardiographic changes is not of very great importance. But a closer study of this can easily be made in this series, as each of the electrocardiographic waves and segments is measured for closer studies.

The relationship of electrocardiographic changes to body weight is not investigated more closely in this monograph, as the study of the literature has given little information on the influence of overweight upon the left ventricular hypertrophy pattern with the exception of a high prevalence of left axis deviation. In a selected series of 157 men between 18 and 25 years and 233 men between 45 and 55 years all entirely healthy and normal by detailed clinical and laboratory examinations, Simonson & Keys (209) found a significant difference in the R and T waves and QRS axis and in general the influence of relative body weight was more prominent in the older than in the younger men. There were similarities between the action of age and relative body weight in regard to the electrocardiogram, and the authors

concluded that an age and weight correction is necessary for a more precise definition of normal electrocardiographic standards. Simpson, on the other hand, did not find any consistent relationship between body weight and the pathological electrocardiographic changes, nor did Leshman find that the frequency of the electrocardiographic abnormalities was affected by obesity in his series.

The influence of age upon left axis deviation is marked in women in the low blood pressure groups, and this is seen both in the diastolic and in the systolic pressure classification of the series (see Figs. 7 18 and 7 19). This influence of age is also seen in the men classified by systolic pressure, but to a minor degree. The increase of left axis deviation with age is partly abolished in the higher blood pressure groups, while there is a steadily increasing frequency of the left ventricular hypertrophy pattern with age. The sum of the left axis deviation and the left ventricular hypertrophy pattern, however, shows a steady increase with age in both sexes in both classifications of the series. This is seen in all blood pressure groups except for the highest, as mentioned above. Here the frequency of left axis deviation shows a decrease with age in the females, but not in the men.

This finding may point to a relationship between the left axis deviation and the left ventricular hypertrophy pattern. Grant (82) has recently assessed the role of left ventricular hypertrophy in the production of left axis deviation in a correlation study between the electrocardiographic and the pathologico-anatomical findings. He found that neither variation in body build nor variation in the anatomical position of the heart could alone be responsible for left axis deviation. The commonest causes of the uncomplicated left axis deviation were chronic coronary artery disease in elderly patients, and left ventricular hypertrophy. The left axis deviation of hypertrophy could, according to Grant (83) be easily differentiated from that of the chronic arteriosclerotic type, because the QRS



complexes are greatly increased in amplitude in all leads in the presence of left ventricular hypertrophy. Grant believes that it is not the hypertrophy itself that produces the axis deviation, but a conduction defect in the left ventricle. Scott (204) in his survey states that in our present state of knowledge, it would appear that abnormal degrees of axis deviation are of importance in the electrocardiographic evaluation of ventricular hypertrophy and, therefore, axis deviation should be determined. When grouping the electrocardiograms in this series, however, no differentiation has been made between the different degrees of left axis deviation by the vector method. A more specific study of this should be undertaken.

In the survey of the literature it has been shown that false positive electrocardiograms, also left ventricular hypertrophy in the absence of noticeable electrocardiographic changes, can both occur. One must therefore not regard the findings in this series as a precise expression of left ventricular hypertrophy. In the groups with low blood pressure in the reduced series these hypertrophy findings appear very occasionally. Thus among women in the lowest blood pressure group (classified by systolic or diastolic pressure) criteria of left ventricular hypertrophy occur in 1 individual and in men in 2 individuals among the youngest age group. Whether these findings are an expression of false positive electrocardiograms or diagnostic failure (cardiac valvular disease) or is not clear. The occurrence of left ventricular hypertrophy among the old men with low blood pressure seems reasonable from the findings above.

This epidemiological study does not give any explanation of the electrocardiographic changes encountered in ventricular hypertrophy. It has only shown some trends pointing to a definite influence of blood pressure and age upon the conventional criteria of left ventricular hypertrophy. The mechanisms that are responsible for the electrocardiographic patterns

in ventricular hypertrophy are not clear but various explanations have been offered. The precise electrophysiologic mechanisms, however, must await further investigations. To give a review of some of the currently accepted views lies outside the scope of this monograph. A survey of the more commonly accepted hypotheses has recently been published by Scott (204).

### Summary

The electrocardiographic findings indicating left ventricular hypertrophy have been based upon the following

- 1 High amplitude in the QRS complex in the precordial leads.
- 2 Changes in the ST-T segment and the T wave over the left ventricle and in lead I combined with left axis deviation.
- 3 Increased duration of the QRS complex to 0.12 sec. and delayed activation time.

(Further details of the criteria are given on p. 184.) Left axis deviation without other signs has been recorded as a separate finding.

The electrocardiogram was recorded on all individuals using 3 bipolar limb leads and 6 unipolar precordial leads. The unipolar limb leads are not included in this study. The number of electrocardiograms not registered or technically erroneous was very small (0.4%). Left bundle branch block, occurring in 0.6% of men and 0.4% of women, is included in this series.

The reduced series (Table 7.1 subgroup 2) shows an increase in the frequency of left ventricular hypertrophy with rising blood pressure in both sexes. In each of the blood pressure groups a considerable increase is seen with age (Figs. 7.18 and 7.19). In the blood pressure group  $\geq 120$  mm Hg diastolic, signs of left ventricular hypertrophy occur in 50-60% of men and women over 40 years of age.

The  $\chi^2$  test shows a significant difference between the blood pressure groups

in both sexes in the two classifications. There is also a significant difference between the age groups except in the case of men on diastolic classification.

The frequency of left ventricular hypertrophy in the non-labile groups is slightly but not significantly higher than in the labile groups in both sexes.

Isolated left axis deviation increases with age in both sexes in the low blood pressure groups. This increase with age is partly abolished in the higher blood pres-

sure groups, while a steady increase of the hypertrophy pattern is seen. The sum of isolated left axis deviation and hypertrophy pattern increases with age and blood pressure. The possibility of a relationship between left axis deviation and left ventricular hypertrophy is discussed.

Furthermore, the possibility of false positive electrocardiograms and also of left ventricular hypertrophy in the absence of noticeable electrocardiographic changes is discussed.

## CHAPTER VIII

# The radiological examination of the heart size

### Description of the method

#### *A survey and a review of the literature*

It lies beyond the scope of this study to give a survey of the methods previously used in the radiological estimation of the heart size whether it is based upon one two- or three-dimensional measurements. It is generally agreed that the three-dimensional measurement is the best method. Several modifications in the technique have been developed in the last 20 years, giving fairly simple methods suitable for routine work and also suitable for certain types of mass survey.

These modifications were first worked out by Swedish radiologists, and they are mainly based upon methods previously described by Rohrer (196) in 1916 and by Kahlström (109) in 1932. Thus Liljeström, Lysholm, Nylén & Zachrisson (128) developed a technique for biplane radiography. They assumed the heart to have a form of an ellipsoid and calculated the frontal area on the basis of an ellipse formulae. These authors, as well as Lysholm, Nylén & Quarnaa (134) related the heart volume to body surface by height and weight according to Du Bois's formula. They found in a selected series of 70 healthy medical male students from 21 to 30 years of age a relative mean heart volume of  $372 \pm 59$  ml (st dev) and in 31 bank-clerks aged 32-47 years a mean heart volume of  $395 \pm 46$  ml.

In practical work it is difficult to measure the transverse axis in the heart ellipsoid since the lower end of the transverse

axis often disappears in the liver shadow. Jonzell (107) in his modification measured the long diameter (L) from the junction between the aorta and the right atrium to the left lower pole and the broad diameter (B) from the right basal border of the cardiac silhouette to the junction between pulmonary conus and the left ventricle. The sagittal diameter (D) is measured from the posterior contour of the sternum to the oesophagus. Jonzell simplified the method of simultaneous exposure in sagittal and frontal directions for practical use by taking the lateral view in the usual way with a 90° rotation of the patient at the same distance immediately after the frontal projection.

Jonzell's calculation of the heart volume in routine work is based upon the formulae  $V = k \times L \times B \times D$ . The constant  $k$  is found to be practically 0.42 at 1.5 m focus-film distance in both directions. Jonzell found that in his series the heart volume figure per sq m body surface showed considerably less individual variations. In the majority of normal people this figure varied between 300 and 400 ml with a minimum of 240 ml and a maximum of 450 ml. Some other experience of normal and pathological cases 450 ml per square metre body surface seems to be the maximum of normal heart size. Jonzell emphasized that these values are to be considered as a heart volume index rather than as a precise measurement of the heart volume. However it is not clear in Jonzell's own work what his normal values are based on.

During the last years several series based on this radiological estimation of the heart size have been published and the following survey of the literature deals only with the method of Liljestrand and co-workers or the modification of Jonell.

Denstad (49) demonstrated a clear difference in the heart volume between the two sexes. The series included in all 377 hospital patients, 152 men and 225 women between 16 and 82 years of age (average 52 years). Forty-five men and 60 women showed no evidence of cardiac disease, the average heart volume in this group being  $378 \pm 77$  ml in the men and  $322 \pm 50$  ml in the women. Any estimation of the heart volume in relation to age was not carried out. The rest of the series suffered from heart disease in different stages of failure.

Afraeta, Nylin & Solberg (145) correlated the heart volume to age, body weight, and oxygen consumption in a series of 763 healthy persons (387 male and 376 female) between 9 and 66 years of age (average 35 years). All cases were submitted many times to observation in hospital and were on these occasions found to be free from any signs of heart or lung disease or of excessive weight. The mean relative heart volume in males was  $390 \pm 89$  ml (st. dev.) and in females 341.52 ml. Björk, Vendsalu & Johansson (25) compared the heart volumes of 224 outpatients with 'functional' heart disorders with those of a control group of 688 patients, derived from a series of X-ray films, in which the heart had been considered to be roentgenologically normal. Both groups showed a clear difference in heart volume between the sexes. The control group showed an increase from 378 ml in men aged 30-39 to 458 ml in the age group 80-89. The corresponding figures in women were 330 and 384 ml in the age group 70-79. No figures of the heart volume in relation to blood pressure are given in these two series.

Josephson (108) did not find any demonstrable correlation between the du-

ration or severity of hypertension and the size of the heart in a series of 80 hypertensive hospital patients selected in accordance with the criteria reported by Master and co-workers. Nor did the stable or unstable nature of hypertension seem to be of any major significance. The criteria of unstable hypertension was a fall of the blood pressure  $\leq 150/90$  measured during the day while staying in hospital.

Amundsen (7) found in a heterogeneous out patient and hospital series including 358 men and 397 women no evidence of heart disease in 39 men and 58 women, while the rest suffered from organic heart disease and other diseases considered liable to influence the heart volume. A difference in the heart volume between the two sexes was found in each of the three groups 20-39, 40-59, and 60 years and over. The relative heart volume in men was estimated to be 131% (rel. vol. women) — 63 ml/m. There was a marked increase with age in all diseased groups, while the normals showed only a slight increase from the age 40-59 to 60 and higher. The author emphasized that although the general trend is towards an increase with age, the variation was found to be different in the different groups. It is felt that the influence of age on the mean relative volume must be due to different factors acting in different ways in the lower and higher age groups. One group of this series was referred for heart volume estimation because of hypertension (160/90 or more) without any evidence of cardiac or renal disease. The patients were subgrouped into severely elevated blood pressure (diastolic blood pressure found never to be 100 or below or highest pressure recorded more than 200/110) while the rest were labelled moderate hypertension. The mean heart size of subjects in these two groups was found to be very similar in both sexes and at all ages. A comparison with the normals' showed that the estimates of the percentage increase were found to be 107 128

and 118 % respectively in the age groups 20-39 40-59 and 60 years and over. Only that for the middle age group was found to be statistically significant. However, since all age groups show a higher mean for hypertensive patients than for normal persons we must take this as an indication that elevated blood pressure is associated with an increase in the relative volume. Another group suffering from coronary disease with or without hypertension showed that coronary disease undoubtedly influenced the heart volume. There were, however, no significant differences between the groups with or without hypertension. Amundsen concludes that there is statistically significant evidence that the average effect of coronary disease is greater than that of elevated blood pressure, and when elevated blood pressure and coronary disease are combined the latter is the deciding factor in the effect upon the relative volume. Nylin (166) states in his last paper on this subject that there is an enormous variation in the heart volume in hypertension both in the compensated and decompensated cases. The series consist of 275 men and 309 women, but no further information is given of the age and blood pressure distribution of the series.

*Error of the method in estimating the heart volume*

The heart volume varies to some extent throughout the heart cycle and is estimated to be largest at the end of diastole. According to Jonell (107) the size of the heart in a small series of 9 young adults showed a difference between diastolic and systolic volume of 9-23 % of the diastolic value. In 6 out of 9 persons the difference was less than 15 %. A closer study of the heart volume changes during one cardiac cycle is given by Ruotenoja, Linko, Lind & Solberg (193). In a series of 18 healthy young sportsmen the average heart volume changes at rest was 40 ml or 5 % of the mean level. During exercise the

variation increased to almost 9 %. The author concluded that the commonly used roentgenological methods of estimating the heart volume cannot give values accurate enough to enable one to follow the finest details of the heart volume changes during the heart beat. By determinations independent of the heart cycle the difference is largely reduced as the exposures seldom occur simultaneously with the maximal systolic contraction. In relation to the heart cycle this phase is short, and rarely subject to exposure. Amundsen (7) states that the cardiac cycle does not give rise to very much change, as the radiological volume includes the heart as a whole and also the root of the aorta and that of the pulmonary artery. According to Thurn (226) the volume of the adjacent afferent and efferent vessels is approximately 75-130 ml.

Respiration produces variation in the heart size with an increase during the inspiratory phase. With prolonged deep inspiration, however, the heart volume decreases as the intrathoracic pressure increases. Comeau & White (42, 43) estimated the variation of the transverse diameter of the heart to be about 17 % and the variation in the frontal heart area to average 13 % measured at deep inspiration and expiration.

Furthermore, an increased heart rate reduces the heart volume in the upright position. According to Larsson & Kjellberg (117) a reduction of 5-10 % was found at a rate of 100 while an increased heart rate of 120 or more produced a reduction of up to 16 % of the frontal area. The authors consider it necessary that all heart volume determinations should be carried out with the patient horizontal, and they have devised a simple method for clinical use.

Among the technical errors is the difficulty in estimating the heart contours, especially when the lower part of the heart contour is buried under the diaphragmatic shadow. The depth in the sagittal plane can also give difficulties when the

oesophagus deviates from the normal course. In overweight individuals the extracardial fat covers the apex region especially when the film is under-exposed. In cases of kyphoscoliosis and other deformities, or of dislocation of the mediastinum, it may be impossible to measure the diameters. Many radiologists have therefore several objections against the heart volume estimation. An error of 0.5 cm in measuring each of the three diameters gives a difference of 12-15 %. Ordinarily the errors should balance each other.

Many radiologists have analysed the errors of reading the films. Axén, Lindgren & Malmström (10) reported that the heart volume estimation according to the method of Liljestrand and co-workers, gave good conformity in double readings by each of the three radiologists. The coefficient of variation of the volume estimation thus twice obtained varied from 2.1 % to 3.7 %. Double exposure of the same subject gave a sigma of  $\pm 16$  ml of the relative heart volume. The authors concluded that the method in its present form gives quite acceptable values even for scientific work. Denstad found by double exposure in 26 cases a mean difference of 4.8 % while Liljestrand and co-workers found 4.7 % in a series of 10 cases. Corneau & White (42) state that from the technical point of view it seems safe to say that the percentage error will be usually less than  $\pm 10$  per cent in those hearts whose volumes are 700 cc. or less, while a percentage error of  $\pm 10$  per cent to  $\pm 20$  per cent may result in those hearts whose volume is greater than 700 cc.

Amundsen (7) has given a thorough review of the experimental error of the method for the standard technique adopted, and in patients examined during daily routine work. It was found that the error under such conditions was slightly higher than that calculated in previous investigations, which had mainly been dealing with younger normal persons.

Amundsen recommends that only figures from highly experienced observers should be used that measurements should be taken under optimal conditions on dry films, and that observer bias should be reduced by either using figures from one observer only or using the mean of the figures from two observers measuring the films independently. The standard error for the single determination (same observer 1 reading) was found to be 30 ml/sq.m. If the same observer read the films from two examinations, each set once the standard error would be 42 ml/sq.m.

This survey of the literature dealing with the method of Liljestrand and co-workers and the modification of Jonell, shows that the series are composed mostly of hospital- or out-patients. Very few series are studied in countries outside Scandinavia using this method of determination of the heart volume.

None of the series are based upon a random selection of the population or even on occupational or other parts of it.

A significant difference of the heart volume between the two sexes is found, and several series show an effect of age upon the heart volume. However few studies give information of the influence of blood pressure, and in most of these the effect of high blood pressure has been found not to be significant.

The normal variations of the heart volume determination are large and there is a marked overlapping in heart volume between healthy people and those with heart disease. In practical clinical work the heart volume is therefore considered of value only in connection with the findings of fluoroscopy and in relation to symptoms and signs. But the investigators have shown that the method can be regarded as fairly accurate. In spite of several technical errors Scandinavian radiologists consider the method to be of value, even in scientific work.

It seems therefore reasonable to apply the method of heart volume determination

to this series to see whether there is any significant influence of blood pressure and age upon the heart size.

#### *Method and technique applied in this study*

The radiological examination of the heart has been done by the author except in the very few cases where the heart had been radiologically examined while the patient had been in hospital during the last 6 months, or where the present examination had revealed a disease necessitating admission to hospital.

The examination was done in connection with the whole clinical investigation, in most cases at the end of the investigation.

The radiological examination started with a fluoroscopy to obtain information about the configuration and size of the heart, especially the size of the left ventricle, aorta, pulmonary artery and lungs.

The frontal film was exposed at deep inspiration in standing position with the tube centred during fluoroscopy on the middle of the heart. For the lateral films the patient stood with the forearms crossed over his head keeping the chest as vertical as possible. The exposure was made after a barium swallow to obtain contrast of the oesophagus. The pictures were taken with a slightly overpenetrated technique. The focus-film distance in both directions was 1.5 m, according to the technique of Jonell.

The apparatus used was Schönander type VH 2, 4 rectifiers with Schönax tube FAR 10 10 kV fixed anode giving 300 mA at 70 kV and 250 mA at 90 kV. This relatively simple apparatus has given a long exposure time in the frontal plane the exposure time varied from 0.1 to maximum 0.5 seconds for particularly fat and muscular individuals, in the sagittal plane the exposure time varied from 0.3 to 0.8 seconds.

All films were read by the author including the films exposed at other departments. When reading the films care was

taken that the author could not see the results of the blood pressure measurements or the other cardiac findings given in the questionnaires.

#### *Observer variation in reading the film*

In order to evaluate the author's consistency in examining X rays and to assess the consistency of two different observers in reading the X rays, the following experiments were undertaken.

Sixty-six randomly selected pairs of films were read by the author and a second observer (Dr P. St. Aubin) on the same day, using the same type of viewing box. Care was taken that the readers could not compare their method of reading the films or the results of estimating the different diameters. It must be emphasized that this experiment was undertaken several years after the author's first reading of the films and also that the second observer was an experienced radiologist from another country (U.S.A.).

To test whether there is a significant difference between the author's 1st and 2nd reading and between the author's 2nd reading and the second observer's reading, t tests of the differences were performed.

The null hypothesis is that the true difference is zero. The results are given in Table 8.1.

The Table shows that the author's 2nd reading is on the average higher than the first, with a mean difference of 15.5 ml. The second observer shows a tendency for a higher reading than the author's reading with an average difference of 12.5 ml. The t test of the difference between the author's 1st and 2nd reading is significant. Thus, under the null hypothesis that the difference is zero, there is little doubt that the observed average difference of 15.5 ml could arise by chance alone. The 95% confidence limits of the average difference are 7.1 ml and 23.9 ml.

When comparing the author's second reading with that of the second observer

Table 8.1

| Reading     | Mean $\pm$ st. error | Mean diff. between paired read. $\pm$ st. error of diff. | t-test of difference      |
|-------------|----------------------|--|---------------------------|
| Own 1st.    | 420.2 $\pm$ 10.2     | 15.5 $\pm$ 3.7   | 4.2      P < 0.001        |
| 2nd.        | 435.7 $\pm$ 10.6     |  |                           |
| II Observer | 448.2 $\pm$ 11.0     | 12.5 $\pm$ 3.7   | 3.4      0.001 < P < 0.01 |

the difference between the paired readings is also significant. Again, there is little doubt that this average difference of 12.5 ml could arise by chance alone. The 95 % confidence limits are 5.7 ml and 19.3 ml. The difference is higher than would be expected on the null hypothesis.

The standard errors of the three readings are of the same magnitude. When comparing the variances of these 3 series of readings of the films, it will be seen that the *F* ratios between the variance of the author's 1st and 2nd reading,

$$F = \frac{s_1^2}{s_2^2} = \frac{103.6}{111.8} = 0.93 \text{ and between}$$

the author's 2nd reading and that of the second observer

$$F = \frac{111.8}{120.03} = 0.93 \text{ are not significant.}$$

**Conclusions** This study shows that there is a significant difference of the heart volume estimation when the author re-examines pairs of X-rays several years after the original reading of the films. There is also a significant difference between observers.

The method of estimating the heart size seems profoundly sensitive to observer variation.

The relative heart volume (heart volume index) in relation to blood pressure and age

An analysis of the series can become reliable only when the series has been reduced by elimination of individuals in

whom the heart volume may be assumed to have changed as the result of heart disease from causes other than hypertension and arteriosclerosis, or illnesses which influence the size of the heart. Therefore all individuals in whom the investigation has confirmed the presence of rheumatic, thyrotoxic, or syphilitic heart disease, kyphoscoliosis and cor pulmonale have been excluded from the series in the same way as described on p. 121 (see Table 7.1)

Individuals with anemia (hemoglobin under 11 g) pregnancy and thyrotoxicosis have not been included in the series either even if they did not show signs of heart disease.

When the series has been reduced in this way it will still consist of a quite heterogeneous group. Some individuals suffer from secondary hypertension and renal diseases. These individuals, however, are relatively few in this X-ray series. Where in the series, and in which age and blood pressure groups they occur will be seen from Tables 8.2 and 8.3.

Division of the series into 6 age groups, regardless of the blood pressure grouping in the different sexes, shows that the heart volume index increases with age. This is shown in Fig. 8.1 p. 204.

The increase with age seems quite linear in women, while the men show a slight S-shaped curve. Dividing the series in this way however does not give an adequate measure of the relationship of the heart volume to age, as it hides the influence of blood pressure. In the same way a division



Table 6. Volume index (Percent)

| Diast. BP | Group | Females     |          |          |          |          |          |          | Males      |          |          |          |          |          |          |     |
|-----------|-------|-------------|----------|----------|----------|----------|----------|----------|------------|----------|----------|----------|----------|----------|----------|-----|
|           |       | Age groups  |          |          |          |          |          |          | Age groups |          |          |          |          |          |          |     |
|           |       | 15-29       | 30-39    | 40-49    | 50-59    | 60-69    | ≥ 70     | Total    | 15-29      | 30-39    | 40-49    | 50-59    | 60-69    | ≥ 70     | Total    |     |
| ≤ 85      | A     | No.         | 13       | 30       | 18       | 19       | 11       | 10       | 101        | 47       | 33       | 16       | 15       | 11       | 8        | 130 |
|           |       | Mean ± s.e. | 344 ± 19 | 363 ± 8  | 372 ± 15 | 393 ± 9  | 396 ± 24 | 389 ± 19 | 375        | 413 ± 9  | 409 ± 8  | 420 ± 21 | 436 ± 17 | 491 ± 35 | 501 ± 29 | 427 |
|           |       | St. d.      | 65       | 46       | 62       | 40       | 75       | 58       |            | 50       | 45       | 60       | 64       | 110      | 77       |     |
| 90-100    | B     | No.         | 19       | 13       | 17       | 10       | 19       | 13       | 101        | 14       | 11       | 19       | 15       | 22       | 15       |     |
|           |       | Mean ± s.e. | 344 ± 19 | 363 ± 8  | 372 ± 15 | 393 ± 9  | 396 ± 24 | 389 ± 19 | 375        | 413 ± 9  | 409 ± 8  | 420 ± 21 | 436 ± 17 | 491 ± 35 | 501 ± 29 | 427 |
|           |       | St. d.      | 65       | 46       | 62       | 40       | 75       | 58       |            | 50       | 45       | 60       | 64       | 110      | 77       |     |
| 105-115   | A     | No.         | 37       | 35       | 59       | 67       | 73       | 58       | 409        | 189      | 81       | 63       | 46       | 51       | 23       | 353 |
|           |       | Mean ± s.e. | 350 ± 7  | 335 ± 5  | 373 ± 7  | 378 ± 6  | 419 ± 10 | 419 ± 8  | 394        | 414 ± 6  | 419 ± 6  | 423 ± 7  | 418 ± 10 | 478 ± 10 | 503 ± 28 | 433 |
|           |       | St. d.      | 44       | 41       | 57       | 59       | 88       | 62       |            | 57       | 52       | 59       | 60       | 75       | 130      |     |
| ≥ 120     | B     | No.         | 15       | 12       | 15       | 16       | 21       | 15       | 14         | 13       | 14       | 17       | 15       | 26       |          |     |
|           |       | Mean ± s.e. | 354 ± 7  | 337 ± 6  | 366 ± 7  | 378 ± 6  | 423 ± 10 | 419 ± 9  | 384        | 413 ± 6  | 419 ± 6  | 425 ± 7  | 417 ± 11 | 475 ± 10 | 489 ± 25 | 431 |
|           |       | St. d.      | 45       | 40       | 57       | 58       | 87       | 63       |            | 57       | 53       | 59       | 70       | 68       | 101      |     |
| 105-115   | A     | No.         | 12       | 11       | 18       | 15       | 20       | 15       | 14         | 14       | 13       | 14       | 17       | 14       | 21       |     |
|           |       | Mean ± s.e. | 285      | 351 ± 11 | 390 ± 10 | 412 ± 12 | 415 ± 12 | 435 ± 14 | 401        | 424 ± 16 | 414 ± 21 | 433 ± 11 | 438 ± 16 | 525 ± 19 | 488 ± 18 | 403 |
|           |       | St. d.      | 48       | 48       | 67       | 77       | 72       | 77       |            | 36       | 63       | 49       | 74       | 93       | 79       |     |
| ≥ 120     | B     | No.         | 15       | 15       | 44       | 39       | 39       | 30       | 168        | 6        | 8        | 22       | 23       | 23       | 20       | 102 |
|           |       | Mean ± s.e. | 285      | 375 ± 16 | 376 ± 10 | 412 ± 13 | 414 ± 12 | 438 ± 14 | 402        | 424 ± 16 | 432 ± 22 | 433 ± 11 | 438 ± 16 | 520 ± 20 | 488 ± 18 | 406 |
|           |       | St. d.      | 38       | 38       | 67       | 79       | 73       | 76       |            | 36       | 57       | 49       | 74       | 93       | 79       |     |
| ≥ 120     | A     | No.         | 1        | 8        | 27       | 37       | 28       | 21       | 122        | 4        | 4        | 19       | 17       | 11       | 3        | 54  |
|           |       | Mean ± s.e. | 369      | 416 ± 25 | 422 ± 17 | 428 ± 12 | 444 ± 13 | 456 ± 16 | 434        | 411 ± 7  | 451 ± 14 | 451 ± 14 | 515 ± 16 | 527 ± 25 | 470 ± 36 | 485 |
|           |       | St. d.      | 60       | 60       | 88       | 71       | 69       | 71       |            | 13       | 13       | 56       | 63       | 70       | 34       |     |
| ≥ 120     | B     | No.         | 4        | 24       | 35       | 25       | 19       | 107      | 3          | 3        | 18       | 16       | 11       | 5        | 51       |     |
|           |       | Mean ± s.e. | 413 ± 21 | 414 ± 17 | 420 ± 11 | 447 ± 14 | 455 ± 17 | 431      | 410 ± 10   | 430 ± 14 | 508 ± 15 | 527 ± 25 | 470 ± 36 | 484      |          |     |
|           |       | St. d.      | 57       | 84       | 65       | 68       | 74       | 74       |            | 14       | 14       | 59       | 59       | 79       | 54       |     |
| Total     | B     | No.         | 9        | 20       | 15       | 15       | 15       | 16       | 16         | 5        | 5        | 15       | 12       | 15       | 12       |     |
|           |       | Mean        | 46       | 101      | 181      | 177      | 145      | 115      | 765        | 141      | 120      | 119      | 99       | 94       | 52       | 625 |
|           |       | St. d.      | 547      | 561      | 577      | 595      | 473      | 428      | 393        | 414      | 417      | 420      | 440      | 496      | 489      | 440 |

Group A denotes the series reduced of heart diseases from causes other than hypertension and arteriosclerosis and Group B denotes the series further reduced of secondary hypertension and renal diseases.

Table 2.2. Heart volume index (l/min/m<sup>2</sup>)

| Syst. BP | Group | Females     |          |          |          |          |          |       | Males      |          |          |          |          |          |       |
|----------|-------|-------------|----------|----------|----------|----------|----------|-------|------------|----------|----------|----------|----------|----------|-------|
|          |       | Age groups  |          |          |          |          |          |       | Age groups |          |          |          |          |          |       |
|          |       | 15-29       | 30-39    | 40-49    | 50-59    | 60-69    | ≥ 70     | Total | 15-29      | 30-39    | 40-49    | 50-59    | 60-69    | ≥ 70     | Total |
| 145      | A     | No.         | 30       | 30       | 27       | 14       | 7        | 147   | 65         | 56       | 38       | 27       | 17       | 6        | 209   |
|          |       | Mean ± s.e. | 345 ± 10 | 356 ± 7  | 368 ± 10 | 388 ± 9  | 390 ± 23 | 367   | 415 ± 6    | 418 ± 7  | 420 ± 11 | 420 ± 13 | 465 ± 24 | 442 ± 25 | 422   |
|          |       | St. d.      | 53       | 42       | 44       | 66       | 35       | 367   | 51         | 50       | 66       | 65       | 97       | 56       | 367   |
| 150-175  | B     | No.         | 16       | 1        | 11       | 17       | 14       | 59    | 12         | 12       | 16       | 15       | 21       | 13       | 89    |
|          |       | Mean ± s.e. | 345 ± 10 | 358 ± 7  | 356 ± 10 | 368 ± 9  | 390 ± 23 | 366   | 415 ± 6    | 418 ± 7  | 420 ± 11 | 420 ± 13 | 465 ± 24 | 442 ± 25 | 422   |
|          |       | St. d.      | 54       | 43       | 44       | 66       | 35       | 366   | 51         | 49       | 66       | 65       | 97       | 56       | 366   |
| 180-205  | A     | No.         | 21       | 33       | 52       | 71       | 20       | 301   | 71         | 59       | 47       | 36       | 37       | 19       | 269   |
|          |       | Mean ± s.e. | 355 ± 10 | 356 ± 6  | 369 ± 6  | 378 ± 7  | 402 ± 13 | 375   | 416 ± 7    | 417 ± 7  | 436 ± 9  | 415 ± 12 | 501 ± 14 | 521 ± 27 | 438   |
|          |       | St. d.      | 45       | 47       | 57       | 55       | 37       | 375   | 62         | 53       | 61       | 70       | 83       | 116      | 438   |
| 180-205  | B     | No.         | 13       | 12       | 15       | 14       | 14       | 68    | 16         | 12       | 14       | 17       | 16       | 16       | 92    |
|          |       | Mean ± s.e. | 349 ± 10 | 358 ± 6  | 368 ± 6  | 377 ± 7  | 399 ± 13 | 375   | 386 ± 7    | 419 ± 7  | 436 ± 9  | 415 ± 12 | 501 ± 14 | 508 ± 20 | 430   |
|          |       | St. d.      | 44       | 42       | 55       | 54       | 37       | 375   | 62         | 53       | 61       | 72       | 83       | 79       | 430   |
| 180-205  | A     | No.         | 13       | 12       | 15       | 14       | 14       | 68    | 16         | 12       | 14       | 17       | 16       | 16       | 92    |
|          |       | Mean ± s.e. | 370 ± 11 | 392 ± 14 | 402 ± 9  | 418 ± 12 | 423 ± 9  | 409   | 389 ± 24   | 391 ± 16 | 420 ± 11 | 485 ± 17 | 496 ± 9  | 510 ± 23 | 466   |
|          |       | St. d.      | 38       | 86       | 61       | 93       | 67       | 409   | 54         | 48       | 51       | 51       | 44       | 104      | 466   |
| 180-205  | B     | No.         | 11       | 11       | 20       | 19       | 16       | 67    | 13         | 12       | 13       | 16       | 14       | 20       | 92    |
|          |       | Mean ± s.e. | 374 ± 13 | 384 ± 13 | 402 ± 9  | 421 ± 13 | 428 ± 9  | 409   | 389 ± 24   | 395 ± 17 | 417 ± 12 | 480 ± 16 | 497 ± 15 | 510 ± 23 | 465   |
|          |       | St. d.      | 41       | 77       | 62       | 95       | 67       | 409   | 54         | 49       | 52       | 52       | 44       | 104      | 465   |
| ≥ 210    | A     | No.         | 5        | 31       | 39       | 39       | 38       | 153   | 13         | 12       | 13       | 16       | 14       | 20       | 103   |
|          |       | Mean ± s.e. | 424 ± 35 | 419 ± 16 | 436 ± 14 | 450 ± 12 | 451 ± 12 | 439   | 423 ± 10   | 423 ± 10 | 451 ± 16 | 473 ± 16 | 527 ± 23 | 441 ± 16 | 477   |
|          |       | St. d.      | 70       | 87       | 89       | 72       | 72       | 439   | 14         | 14       | 54       | 54       | 92       | 44       | 477   |
| ≥ 210    | B     | No.         | 1        | 1        | 28       | 34       | 35       | 134   | 1          | 1        | 13       | 13       | 16       | 8        | 51    |
|          |       | Mean ± s.e. | 441 ± 16 | 429 ± 13 | 433 ± 12 | 450 ± 13 | 450 ± 13 | 437   | 416        | 416      | 451 ± 16 | 473 ± 16 | 517 ± 22 | 441 ± 16 | 475   |
|          |       | St. d.      | 111      | 88       | 72       | 72       | 75       | 437   | 1          | 1        | 54       | 54       | 87       | 44       | 475   |
| ≥ 210    | B     | No.         | 20       | 20       | 20       | 20       | 17       | 134   | 1          | 1        | 12       | 11       | 17       | 10       | 51    |
|          |       | Mean ± s.e. | 441 ± 16 | 429 ± 13 | 433 ± 12 | 450 ± 13 | 450 ± 13 | 437   | 416        | 416      | 451 ± 16 | 473 ± 16 | 517 ± 22 | 441 ± 16 | 475   |
|          |       | St. d.      | 111      | 88       | 72       | 72       | 75       | 437   | 1          | 1        | 54       | 54       | 87       | 44       | 475   |

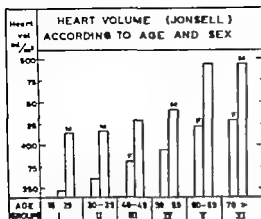


Fig. 8.1 The relative heart volume (heart volume index) related to age and sex. The increase with age is almost linear in women, while in men there is a marked increase from the age group 50-59 to 60-69.

of the series into blood pressure groups, whether this is done according to a systolic or a diastolic classification, as shown in Fig. 8.2 hides the influence of age.

In Tables 8.2 and 8.3 the reduced series is divided into 6 age groups and 4 blood pressure groups, classified by systolic and diastolic pressure according to measurements taken in the sitting position. In these Tables the series has been divided into two groups. Group A includes secondary hypertension and renal diseases, while in group B these individuals are excluded.

There is on the whole very little difference in the mean values and in the scatter between the corresponding groups A and B. Thus the mean values of the heart volume index is very slightly influenced by secondary hypertension and renal diseases in this series.

When comparing the mean values in the same blood pressure group of the series B, one finds an even increase with age in both sexes. This increase in heart volume index is to be seen in all blood pressure groups, whether the material is classified by systolic or diastolic pressure. An exception however is seen in the

highest age group ( $\geq 70$ ) in men. Here we find a fall in the higher blood pressure groups 105-115 and  $\geq 120$  mm Hg diastolic and  $\geq 210$  mm Hg systolic. This fall in the highest age group cannot be seen in women.

When considering the mean values in the same age group in relation to increasing blood pressure (vertical view of the Table) we also find a tendency to increase but this tendency is ambiguous. The heart volume index is slightly higher in the blood pressure group  $\leq 85$  mm diastolic than in the 90-100 mm group in some of the middle age groups in both sexes. When classified by systolic pressure the mean values in the age group 50-59 in both sexes are slightly higher in the group  $\geq 145$  mm than in the 150-175 mm group.

To throw light on the variation around the mean values, Tables 8.2 and 8.3 give the standard error of the mean, the standard deviation and the coefficient of variation. The variation, expressed by the standard deviation, increases somewhat with age, in men as well as in women. Thus in men the standard deviation varies from about 50 ml in the younger to 80-90 ml in the higher age groups, with a maximum of

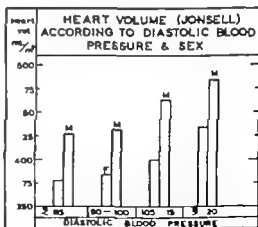


Fig. 8.2. The heart volume index shows fairly even increase when the series is divided according to blood pressure.

116 ml in one particular age group. In women the standard deviation shows a corresponding variation from about 40 to 70-80 ml with a maximum of 95 ml. On the other hand, the standard deviation does not show any consistent increase if one considers the same age group in relation to the increasing blood pressure. However the number of individuals in several groups is small, and one should be careful when making comparisons. As an increase in the heart volume index and increase in the standard deviation have been noticed with higher age, it is natural to express the standard deviation as a percentage of the heart volume index. The coefficient of variation has therefore been calculated, and the values are found to be relatively constant, varying between 12 and 20 % in most of the groups, with a minimum of 3 % in one particular group with few individuals and a maximum of 22 %. There does not seem to be any consistent difference in the coefficient of variation in men and women, except that the values of the coefficient of variation is slightly higher in women in the blood pressure group  $\geq 210$  mm systolic and  $\geq 120$  mm diastolic.

An illustration of the influence of age and blood pressure on the mean values of the heart volume is given in Fig. 8.3.

The Figure shows in women a fairly even increase in the heart volume index with age in all blood pressure groups, giving an almost linear curve. There is a slight but consistent elevation of this curve with higher blood pressure. This holds good whether the series is classified by systolic or diastolic pressure. In men the curves are of a somewhat different shape because of a sharper increase in the mean values from the age 50-59 to 60-69 years. This applies to the diastolic blood pressure groups  $\leq 84$ , 90-100 and 105-115 mm Hg and in the systolic blood pressure groups  $\leq 145$  and 150-175 mm Hg. The mean values show only a slight increase from the youngest age group up to the 50-59 age group in these blood pressure groups. In the blood pressure group 180-205 mm

systolic it can be seen that a sharper increase occurs at an earlier age (fourth decade) and in the highest blood pressure groups ( $\geq 120$  mm diastolic and  $\geq 210$  mm systolic) this increase occurs from 30-39 years. After this rather sharp increase there is a slight flattening off of the level in the mean values in the highest age groups and even a fall in the mean values in the highest blood pressure groups (105-115 and  $\leq 120$  mm diastolic and  $\geq 210$  mm Hg systolic). Thus the mean values of the heart volume index describe a slightly S-shaped curve in men.

#### Statistical analysis

The data given in Table 8.2 and illustrated in Fig. 8.3 suggest a relationship of the heart volume to age and blood pressure. To distinguish between the separate effects of age and of blood pressure the data have been subjected to a multiple regression analysis. The data suggest a linear relationship given in the formula

$$y = a + b_1x_1 + b_2x_2 + b_3x_3$$

where  $y$  = heart volume index,  $x_1$  = age,  $x_2$  = blood pressure and  $x_3 = x_1x_2$  = product of age and blood pressure.

$b_1$  = partial regression coefficient for age,  
 $b_2$  = partial regression coefficient for blood pressure,

$b_3$  = partial regression coefficient for interaction of age and blood pressure.

The term  $b_1$  tells us how much the heart volume ( $y$ ) changes for a unit change in age if both the other  $x$ 's remain constant, and in the same way the term  $b_2$  tells us how much  $y$  changes for a unit change in blood pressure if both the other  $x$ 's remain constant. The term  $b_3$  is a measure of the extent to which the factors age and blood pressure interact, i.e. whether the relationship between heart volume and blood pressure varies from age group to age group.

The assumption is made that all blood pressure groups have the same class interval (15 mm) although the lowest and highest groups are open.

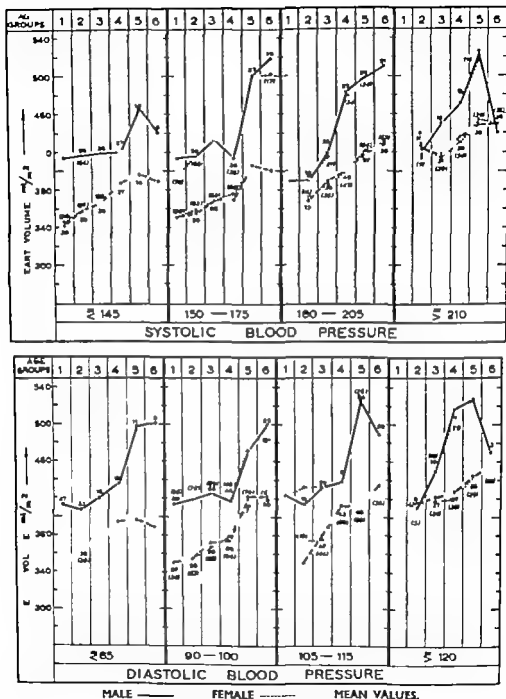


Fig. 6.5 Both figures illustrate the increase of the mean values of the relative heart volume with increasing age and blood pressure. In women the increase with age is fairly even in all blood pressure groups, while in men the curves show a change in the slope giving a more S-shaped curve, with fall of the mean values in the highest age group with high blood pressure.

Table 8.4

|                   | S. sq     | D. L. | M. sq   | V. R.              |
|-------------------|-----------|-------|---------|--------------------|
| Women             |           |       |         |                    |
| Due to regression | 583.437   | 3     | 191.140 | 43.33% $P < 0.001$ |
| About regression  | 3,788.332 | 61    | 4.308   |                    |
| Total             | 3,866.789 | 64    |         |                    |
| Men               |           |       |         |                    |
| Due to regression | 51,456    | 3     | 180,818 | 58.32% $P < 0.001$ |
| About regression  | 2,930,015 | 621   | 4.718   |                    |
| Total             | 3,472.51  | 624   |         |                    |

The results of the calculations of the partial regression coefficients are given in Table 8.5. To test whether the three regression coefficients differ significantly from zero, an analysis of variance has been undertaken.

From these calculations the standard errors of the three partial regression coefficients have been worked out by means of the formula  $SEb_i = \sqrt{s^2 C}$  where  $s^2$  represents the mean square about regression and  $C_i$  the multiplier for the  $i$ th partial regression coefficient (see Snedecor 215). The  $t$  tests for the significance of the partial regression coefficients are also given in Table 8.5.

**Conclusion.** Both the partial regression coefficients,  $b_1$  (for age) and  $b_2$  (for blood pressure) are significant which shows that both the independent variables  $x_1$  (age) and  $x_2$  (blood pressure) exert an effect on heart volume. On the other hand the interaction term  $b_3$  is non-significant in both sexes.

The variate  $x_3$  ( $x_1 x_2$ ) can be omitted from the analysis because the regression on interaction is small and non-significant. However this will change the other partial regression coefficients. A new analysis of variance based upon the reduced number of variates has therefore been worked out.

Table 8.5

| Sex   | Partial regression coefficients $\pm$ st. error | $t$ -test                             |
|-------|---|---------------------------------------|
| Women | $b_1$ 16.59 $\pm$ 1.93                          | 8.61 $\infty$ $P < 0.001$             |
|       | $b_2$ 13.50 $\pm$ 3.25                          | 4.15 $\infty$ $P < 0.001$ 761 degrees |
|       | $b_3$ -1.74 $\pm$ 2.19                          | 0.8 0.5 $< P < 0.4$ of freedom        |
| Men   | $b_1$ 15.68 $\pm$ 1.82                          | 8.62 $\infty$ $P < 0.001$             |
|       | $b_2$ 8.17 $\pm$ 3.64                           | 2.24 0.02 $P < 0.05$ 621 degrees      |
|       | $b_3$ 4.04 $\pm$ 2.17                           | 1.86 0.05 $< P < 0.10$ of freedom     |

The partial regression coefficients for age ( $b_1$ ), blood pressure ( $b_2$ ) and interaction of age and blood pressure ( $b_3$ ). The  $t$ -tests for significance of the partial regression coefficients are also given.

If the variate of  $b$  is deleted the sum of squares due to regression is reduced by the quantity given by the formula  $b \cdot C_{22}$

This gives 2,714 for women and 16,284 for men. A new analysis of variance due to regression gives the following

Table 8.6

|                   | S. sq     | D f | M sq    | V R.        |
|-------------------|-----------|-----|---------|-------------|
| <b>Women</b>      |           |     |         |             |
| Due to regression | 585.723   | 2   | 292.862 | 68.01       |
| About regression  | 3,281.066 | 762 | 4.306   | $P < 0.001$ |
| Total             | 3,866.789 | 764 |         |             |
| <b>Men</b>        |           |     |         |             |
| Due to regression | 540.653   | 2   | 270.327 | 57.35       |
| About regression  | 2,931.818 | 622 | 4.714   | $P < 0.001$ |
| Total             | 3,472.471 | 624 |         |             |

The new partial regression coefficients have been worked out according to the formulae given by Snedecor (215)

$$\text{new } b = \text{old } b - \frac{C_{22} \cdot b}{C_{22}} \text{ and new } b = \frac{C_{22} \cdot b}{C_{22}}$$

Further the multipliers have been corrected and finally the standard error of the two partial regression coefficients has been calculated according to the formulae given previously. The results are given in Table 8.7. The results of the final t-test are also given in the same Table.

The multiple regression equation is

$$Y = y - b(x - \bar{x}) + b(x - \bar{x})$$

where  $y$  represents the grand mean of the heart volume index,  $\bar{x}$  the mean age and  $\bar{x}$  the mean diastolic blood pressure in working units. When putting the resultant values into this formula one obtains the following

$$\text{Women } Y = 15.90x + 12.18x + 376$$

$$\text{Men } Y = 16.21x + 9.38x + 438$$

The equation tells that for each unit of age (10 years) the heart volume index increases by 15.9 ml in women and 16.2 ml in men further that the heart volume increases by 12.2 ml in women and 9.4 ml in men for each unit of blood pressure.

From these equations the calculated mean heart volume index is worked out

Table 8.7 The new partial regression coefficients and the test of significance

| Sex   | Partial regression coefficients $\pm$ st. error | t-test   |
|-------|---|--|
| Women | $b$ 15.89 $\pm$ 1.71<br>$b$ 12.18 $\pm$ 2.79    | 9.29*<br>4.36<br>$P < 0.001$ 761 degrees<br>$P < 0.001$ of freedom       |
| Men   | $b$ 16.21 $\pm$ 1.82<br>$b$ 9.38 $\pm$ 3.55     | 8.92<br>2.65<br>$P < 0.001$ 621 degrees<br>0.001 $< P < 0.01$ of freedom |

Table 8.8. Mean heart volume index  
Observed and calculated values

| Diastolic<br>BP | Age   |       |       |       |       |     |
|-----------------|-------|-------|-------|-------|-------|-----|
|                 | 15-29 | 30-39 | 40-49 | 50-59 | 60-69 | ≥ 0 |
| Men             |       |       |       |       |       |     |
| ≤ 85            | No.   | 47    | 33    | 16    | 11    | 8   |
|                 | Obs.  | 413   | 409   | 420   | 436   | 494 |
|                 | Calc. | 396   | 41    | 429   | 445   | 461 |
| 90-100          | No.   | 88    | 76    | 63    | 45    | 49  |
|                 | Obs.  | 413   | 419   | 425   | 417   | 474 |
|                 | Calc. | 406   | 421   | 438   | 454   | 470 |
| 105-115         | No.   | 6     | 8     | 22    | 23    | 20  |
|                 | Obs.  | 424   | 432   | 433   | 438   | 529 |
|                 | Calc. | 415   | 431   | 447   | 463   | 480 |
| ≥ 120           | No.   |       | 3     | 10    | 11    | 3   |
|                 | Obs.  |       | 410   | 450   | 509   | 527 |
|                 | Calc. | 424   | 440   | 457   | 473   | 489 |
| Women           |       |       |       |       |       |     |
| ≤ 85            | No.   | 13    | 29    | 18    | 19    | 11  |
|                 | Obs.  | 348   | 363   | 372   | 395   | 396 |
|                 | Calc. | 332   | 348   | 364   | 380   | 396 |
| 90-100          | No.   | 34    | 33    | 83    | 84    | 70  |
|                 | Obs.  | 350   | 357   | 369   | 378   | 423 |
|                 | Calc. | 345   | 360   | 376   | 392   | 408 |
| 105-115         | No.   | 1     | 15    | 44    | 39    | 39  |
|                 | Obs.  | 285   | 352   | 376   | 412   | 414 |
|                 | Calc. | 357   | 373   | 389   | 405   | 419 |
| ≥ 120           | No.   |       | 4     | 24    | 35    | 25  |
|                 | Obs.  |       | 415   | 414   | 420   | 447 |
|                 | Calc. | 369   | 385   | 401   | 417   | 433 |

for each sex in each of the 24 cells corresponding to combinations of age and blood pressure.

The Table shows that the difference between the mean observed and calculated heart volume is fairly small and non-systematic in most groups.

The full analysis of variance shown in Table 8.9 shows that these deviations (represented by the two residuals between cells) are non-significant for females but are significant for males.

In men in the age group 40-49 years there is a systematic negative difference and in the 60-69 years age group systematic positive difference. This feature may be seen from Fig. 8.3 which shows a change in the slope of the curve in men, while the curves are almost linear in women. It is therefore of interest to analyse these differences between the observed and calculated mean values further. The question is whether the difference between the age groups 40-49 and 60-69



Table 8.9

|               | S. sq     | D. f. | M. sq   | V. R. |           |
|---------------|-----------|-------|---------|-------|-----------|
| W o m e n     |           |       |         |       |           |
| Between cells | 693,982   | 22    | 31,545  | 7.58* | P < 0.001 |
| Multi. regr   | 585,723   | 21    | 292,861 | 54.1  | P < 0.001 |
| Residual      | 108,259   | 20    | 5,413   | 1.27  |           |
| Within cells  | 3,172,807 | 74    | 4,276   |       |           |
| Total         | 3,866,789 | 764   |         |       |           |
| M e n         |           |       |         |       |           |
| Between cells | 881,765   | 22    | 40,080  | 9.31  | P < 0.001 |
| Multi. regr   | 525,174   | 21    | 263,087 | 13.5  | P < 0.001 |
| Residual      | 395,592   | 20    | 19,780  | 4.58* | P < 0.001 |
| Within cells  | 2,590,707 | 607   | 4,304   |       |           |
| Total         | 3,472,471 | 624   |         |       |           |

Table 8.10

| BP                          | $\bar{d} \pm SE$ | d. f. | t-test |                 |  |
|-----------------------------|------------------|-------|--------|-----------------|--|
| Males ( $d_1$ )             |                  |       |        |                 |  |
| $\leq 85$                   | 74 $\pm$ 37.9    | 25    | 1.95   | 0.05 < P < 0.10 |  |
| 90-100                      | 49 $\pm$ 12.1    | 110   | 4.03   | P < 0.001       |  |
| 105-115                     | 96 $\pm$ 22.8    | 43    | 4.21   | P < 0.001       |  |
| $\geq 120$                  | 77 $\pm$ 26.7    | 27    | 2.88*  | 0.02 < P < 0.05 |  |
| Females ( $d_2$ )           |                  |       |        |                 |  |
| $\leq 85$                   | 24 $\pm$ 25.7    | 27    |        |                 |  |
| 90-100                      | 34 $\pm$ 11.3    | 163   | 4.8*   | P < 0.001       |  |
| 105-115                     | 38 $\pm$ 15.5    | 81    | 2.43   | 0.02 < P < 0.05 |  |
| $\geq 120$                  | 33 $\pm$ 22.2    | 47    |        |                 |  |
| Male - Female ( $d - d_2$ ) |                  |       |        |                 |  |
| $\leq 85$                   | 50 $\pm$ 45.9    | 54    |        |                 |  |
| 90-100                      | 5 $\pm$ 16.5     | 273   |        |                 |  |
| 105-115                     | 58 $\pm$ 27.6    | 126   | 2.1    | 0.02 < P < 0.05 |  |
| $\geq 120$                  | 44 $\pm$ 34.7    | 76    |        |                 |  |

The Table shows the difference between the heart volume index in the 40-49 and 60-69 age groups in each sex separately and further the difference ( $d - d_2$ ) between the two sexes. The Table also includes the significant tests.

years is significant in each of the blood pressure groups in each sex (difference in men  $\bar{d}$  in women  $\bar{d}_2$ ). Secondly we want to test the significance of the differences between the values  $\bar{d}$  and  $\bar{d}_2$  for the two sexes.

The data are given in Table 8.10 for each sex and blood pressure group separately. The standard error has been calculated according to the formula

$$SE = \sqrt{\left(\frac{1}{n} + \frac{1}{n_2}\right)} \text{ where } n \text{ and } n_2 \text{ are}$$

Table 8.11

| Diastolic<br>BP $\geq 105$ |           | Age   |       |       |       |       |           |
|----------------------------|-----------|-------|-------|-------|-------|-------|-----------|
|                            |           | 15-29 | 30-39 | 40-49 | 50-59 | 60-69 | $\geq 70$ |
| Females                    |           |       |       |       |       |       |           |
| Non-labile                 | No.       | 1     | 11    | 41    | 35    | 26    | 25        |
|                            | $\bar{x}$ | 367   | 405   | 401   | 428   | 435   | 440       |
| Labile                     | No.       | 1     | 12    | 24    | 23    | 25    | 19        |
|                            | $\bar{x}$ | 285   | 350   | 373   | 476   | 411   | 439       |
| Males                      |           |       |       |       |       |       |           |
| Non-labile                 | No.       | 2     | 4     | 14    | 15    | 15    | 6         |
|                            | $\bar{x}$ | 443   | 391   | 439   | 501   | 529   | 507       |
| Labile                     | No.       | 3     | 5     | 17    | 15    | 13    | 11        |
|                            | $\bar{x}$ | 414   | 411   | 424   | 457   | 518   | 463       |

The Table includes the number of individuals (No.) and the mean heart volume index ( ) in the labile and non-labile (stable) blood pressure groups in both sexes.

the numbers of individuals in the two age groups, and  $s^2$  is the pooled estimate of variance within the two age groups, on  $+ n_2 - 2$  degrees of freedom.

Table 8.10 also includes the difference  $d - d_0$  between the values of  $d$  for the two sexes, with the standard error

$$SE = \sqrt{(SE_{d_1})^2 + (SE_{d_2})^2}$$

The Table shows a larger difference in men than in women in nearly all blood pressure groups, and the value  $d$  is significant in all groups, except the lowest ( $0.05 < P < 0.10$ ). This means that the increase in the mean heart volume in men between these age groups is unlikely to occur by chance in most groups. In women the difference is only significant in the two middle blood pressure groups.

The difference  $d - d_0$  between the two sexes is only significant in one blood pressure group ( $0.02 < P < 0.05$ ). There is therefore suggestive but not very strong evidence that the heart volume index for men increases more between 40-49 and 60-69 than in women of the same blood pressure.

*The heart volume index in relation to the lability of the blood pressure*

To study the influence of the blood pressure lability upon the heart volume index, the reduced series has been grouped into a labile and stable (non labile) blood pressure group in the same way as for the previous cardiac findings (see p. 133)

#### 1 High blood pressure group ( $\geq 105$ mm Hg) in sitting position

The data are given in Table 8.11 which shows the mean values of the heart volume index and the number of individuals within each cell in both sexes. There is in all age groups, except one (men 30-39 years) a consistently larger mean heart volume in the stable groups. The difference however is slight on the average 24 ml in women and 20 ml in men. In women one finds the largest difference in the age groups 40-49 and in men 30-59 years of age.

The findings are illustrated in Fig. 8.4 showing the mean heart volume index in each cell in sitting position to the left of the diagram and the subgrouping of the

## RELATIVE HEART VOLUME (JONSELL)

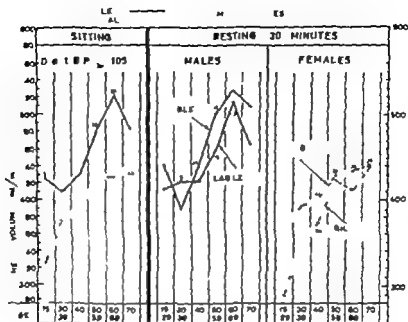


Fig 8.4 The mean values of the heart volume index are consistently larger in the stable (non-labile) groups in both sexes, except 1 men aged 30-39 years.

series into a labile and a stable group (after 30 minutes rest) to the right of the diagram.

#### Statistical analysis

The problem is whether the difference between the mean value is significant in either sex.

The mean difference between the stable and the labile group has been worked out in each cell including the variance of the differences, according to the formula

$\text{var}(\bar{d}) = S^2 \left( \frac{1}{n_s} + \frac{1}{n_l} \right)$  where  $S^2$  represents the pooled  $S^2$  within cells

$$S^2 = \frac{\sum (x - \bar{x})^2 + \sum (\bar{x} - \bar{x})^2}{n - 2}$$

Since the number of individuals in each cell is quite different, each cell has been

given a weight represented by  $w = \frac{1}{\text{var}(\bar{d})}$

and the weighted mean difference ( $\bar{d}$ ) has been calculated using the formula

$$\bar{d} = \frac{\sum w \bar{d}}{\sum w} \quad \text{The variance of the weighted}$$

mean difference  $\text{var}(\bar{d}) = \frac{1}{\sum w}$  and the

$$\text{standard error } SE(\bar{d}) = \sqrt{\text{var}(\bar{d})}$$

The final result of the calculation is given in Table 8.12 presenting the mean and its standard error including the  $t$  test.

There is a significant difference between the labile and the stable blood pressure groups in women but not in men. However this difference could be an interaction between age and blood pressure liability. To test whether there is any significant

Table 8.12.

Mean difference of the heart volume index, including the standard error and the results of the *t*-test

| Sex   | $d \pm S.E.$      | <i>t</i> -test                     |
|-------|-------------------|------------------------------------|
| Women | $24.27 \pm 9.13$  | 2.66 $0.05 < P < 0.02$             |
| Men   | $20.23 \pm 11.38$ | 1.78 $0.2 < P < 0.1$<br>on 5 d. f. |

interaction a  $\chi^2$  test has been worked out according to the formula

$$\chi^2 = \sum (w_i d_i)^2 / \sum w_i^2 \text{ on 5 d. f.}$$

These calculations give

for women  $\chi^2 = 4.46$   $0.50 < P < 0.90$

for men  $\chi^2 = 4.32$   $0.70 < P < 0.50$

i.e. no significant interaction in either sex.

The mean difference of the heart volume index between the labile and the stable groups in women may therefore be independent of age.

## 2. Low blood pressure group ( $\leq 100$ mm Hg) in sitting position

In contrast to the high blood pressure group there is no systematic difference between the labile and the non-labile (stable) groups: thus three age groups show a positive difference and three a negative difference in both sexes. In all the difference is very small, and there would be no point in presenting the data or subjecting the series to any statistical analysis.

## Discussion

When comparing the relative heart volume in this series with the data given in most of the series referred to earlier somewhat higher mean values and also a higher range are found in this series. But a closer comparison can only be made after the data have been adjusted to obtain corresponding age and blood pressure groups in each sex.

The 95% confidence intervals for the arithmetic mean in women aged 20-39 of Amundsen's 'normal series' (7) are 319 and 365 ml/min. In women 40-59 they are 312-352 and 60 or higher 334-426. The corresponding values in men are 356-417 346-400 and 375-500. The present series shows that the adjusted mean values in women are 355 384 and 392 and in men 410, 427 and 496 respectively. Thus in both sexes the mean values in the age groups 40-59 lie outside the limits given for the 95% confidence interval. When comparing the data of Björk and his co-workers (25) one finds that the mean values in women in younger age groups in this series lie slightly above the figures given, but in the age groups 50-59 and 60-69 the differences are somewhat higher (35 and 32 ml respectively). In men the differences between the mean values are higher in the younger age groups 22 and 36 ml respectively while the age groups 60-69 and 70 or higher show a difference of 72 and 92 ml. No estimation of the confidence limits can be made, as sufficient data are not given. When compared with the data given by Liljestrand and his associates (128) based upon healthy medical male students and bank clerks, the present series also shows higher mean values in corresponding age groups. The confidence limits are in the age group 21-32 358-386 and in the age group 32-47 379-411.

The other series referred to earlier do not give sufficient data for closer comparison.

There are several reasons for this difference in the relative heart volume. The main reason is probably that the present series are based upon a population subsample of mostly healthy people including heavy workers, while most of the series referred to earlier are based upon hospital or out patients. It is clearly shown from the series of Grewin (84) that the heavy workers have larger heart volume than intermediate or light workers. The difference between heavy labourers and light workers in Grewin's series was 70

formation on the influence of blood pressure and in most of them the effect has been found insignificant. There is marked overlapping in the heart volume between healthy people and those with heart disease. In clinical work the heart volume is therefore considered of value only in relation to symptoms and signs.

In this survey the radiological examinations have been done and all films read by the author. There is a significant difference in the heart volume index when the author re-examines pairs of X-rays several years after the original reading of the film. There is also a significant difference between observers.

This series, reduced by elimination of individuals in whom the heart volume may be assumed to have changed as the result of heart disease, from causes other than hypertension and arteriosclerosis, or illness which influences the size of the heart, shows that the heart volume index increases with age in all blood pressure

groups, giving an almost linear curve in women. In men the mean values describe a slightly S-shaped curve. There is a slight but consistent elevation of this curve with higher blood pressures. This holds whether the series is classified by systolic or diastolic pressure.

The heart volume index is very little influenced by secondary hypertension and renal diseases.

The statistical analysis shows that for each unit of age (10 years) the heart volume index increases by 16 ml in men and women and by 12 ml in women and 9 ml in men for each unit (15 mm Hg diastolic) of blood pressure.

The influence of the blood pressure liability upon the heart volume index has been investigated. In all age groups, except 30-39 years in men, a consistently larger mean heart volume has been found in the stable groups. However the differences are very slight and only significant in women.

## CHAPTER IX

### Final remarks

Although some of the findings represented in the previous chapters (VI to VIII) have been described in considerable detail, there are still many problems unsolved and several new questions arise.

First of all it has to be emphasized that the findings in this series have only been related to age and blood pressure in each sex separately. It is of great importance to extend the investigation and correlate the findings, for instance the electrocardiographic findings and the heart volume but this has hitherto been set aside, as the analyses would be still more complicated. The investigations should also be extended to correlation studies of other signs, for instance the ophthalmoscopic findings versus the cardiac signs. These correlation studies would complete the picture of the signs and symptoms presented in this study. It has been necessary however to limit the investigation according to the plan of the study.

Among the main questions to be evaluated is the significance of a *casual blood pressure*. In chapter VI a detailed description of the blood pressure findings is presented, and several important points regarding the casual pressure have been discussed. The main difficulty however is to know the practical significance of the casual blood pressure. The advantage of the casual blood pressure is that it is what is usually measured by doctors. Several authors have criticized the use of the casual blood pressure as an index in blood pressure studies. The casual blood pressure is certainly a measurement of limited value

when dealing with individuals or clinical cases, but the criticism becomes less important in epidemiological studies when dealing with groups of individuals (see Pickering 178).

Wilson (235) states "The starting point of epidemiological studies is the validity of blood pressure estimation as an index. Examination of the casual blood pressure should be made to see whether further standardization of technique is possible and what additional criteria can reasonably be included in population studies."

In this study a series of additional blood pressure measurements were taken with the same number of readings on each individual at a specified time interval of half an hour. The third reading has consistently been noted in the sitting and lying positions. In doing so most individuals showed a reduction in the blood pressure, and consequently the momentary fluctuations resulting from emotional responses have to some extent been eliminated. On giving the individuals the opportunity of lying down relaxed for half an hour a further reduction in the blood pressure was found.

The object of this procedure has been to see if a short relaxing period would be of any practical importance. It was shown that the stable groups (non-labile) tended to have a higher prevalence of certain symptoms and signs than the labile groups.

The dividing lines between these two groups are the regression lines presented in Fig. 6.21. The slope of these regression lines is influenced by age and by height

of the blood pressure in both sexes. Therefore it was found illogical to divide the series into labile and non-labile groups by using an arbitrary and constant value of the blood pressure, say 40 mm systolic or 20 mm diastolic, as the dividing line between the two groups (see page 133).

Although this series shows a higher prevalence of most symptoms and signs in the non-labile groups, the statistical analysis gives a significant difference between the labile and non-labile groups in only some of the findings.

Thus the subjective symptom dyspnoea shows somewhat different results in the two sexes. When dividing the series with a blood pressure  $\geq 105$  mm Hg diastolic (in sitting position) there is a significant difference in the prevalence of marked dyspnoea between the labile and non-labile groups in women, but not in men. This is discussed in more detail on p. 137.

An evaluation of the cardiac murmurs stethoscopically is also highly subjective and consequently more liable to intra-observer variation than objective methods. Estimation of the heart size either by measuring the apex beat in cm from the midsternal line, or electrocardiographically using the commonly accepted criteria of left ventricular hypertrophy, or radiologically by estimating the heart volume index, is considered to be more objective. However these methods are also liable to intra-observer and methodical variations. As shown in chapters VII and VIII this series shows a significant difference between the labile and non-labile groups in both sexes when applying all three methods, except for the heart volume index in men.

As a result of this relationship between blood pressure lability and the prevalence of cardiac signs and symptoms it seems reasonable to propose that the technique of blood pressure recording should be standardized by using short resting periods for additional recordings in epidemiological blood pressure surveys. Much work is needed on this elementary question and

the necessity for uniformity in comparative studies with regard to the methodology of blood pressure determinations is obvious.

A second main question is whether the results of this blood pressure study can contribute to the current controversy on the nature of high blood pressure without evident cause.

It has been pointed out by Pickering (179) that the blood pressure levels are distributed continuously in the population. There is therefore no justification for separating essential hypertension and normal pressure by a sharp dividing line. Those with high blood pressure represent one extreme of this distribution and any separation into a hypertensive group and a normotensive group is artificial. In the studies of Hamilton *et al.* (91) and Miall & Oldham (150) (see chapter II) it was found that there is a relationship between the blood pressure of the first-degree relatives and those of their propositi. This relationship is independent of the blood pressure of the propositi. Pickering therefore concludes that the inheritance of blood pressure is probably multifactorial and that the inheritance is of the same kind and of the same degree over the whole blood pressure range. In other words blood pressure is inherited like height, intelligence, and many other traits, as a graded characteristic. Oldham *et al.* (167) put it like this: just as stature, the classical human example of polygenic inheritance, is the sum of a number of separate bones and tissues, so is the arterial pressure the resultant of a number of discrete components of the cardiovascular system.

On the other hand Platt (183) concludes that there is overwhelming evidence against the continuous distribution theory. After re-examining the data of Hamilton *et al.* and of Sobye (216) on essential hypertension he found a bimodality for systolic pressure and probably also for diastolic pressure in siblings of hypertensives aged 45-60. Platt postulates that the rise in mean pressure with age is due to the increasing numbers of individuals with

essential hypertension, and only those with essential hypertension show a rise of blood pressure.

Morrison & Morris (158) analysed the causal blood pressure and the length of life of parents of a sample of the men working as drivers or conductors of London omnibuses, and found that the average rise of systolic pressure during middle age in drivers seemed to be due to a fraction of the men, to the emergence of a minority of individuals from particular families with high blood pressure. The diastolic blood pressures were distributed continuously but further classification showed that this curve of diastolic pressure was in fact made up of two overlapping but quite distinct distributions.

Both Platt, and Morrison & Morris, came to the conclusion that two populations are found, one hypertensive and the other normotensive, in groups selected by an inheritance factor.

Their finding supports the hypothesis that essential hypertension is a specific disease entity and qualitatively different from normal blood pressure. When considering the findings in this series in relation to the hypothesis put forward by Pickering and by Platt, there are some points in favour of the Pickering's hypothesis of unimodality and the quantitative relationship between blood pressure and its effects.

In chapter VI analysis of the blood pressure distributions is given. When the series is grouped into 4 blood pressure groups, based upon a stratification of the systolic blood pressure in 1950 (see Fig. 6.1) the frequency distributions of the systolic blood pressure of the same groups of individuals in 1951-52 are almost symmetrical. Some show a tail to the right, but no evidence of a double peak is to be seen (see Figs. 6.2 and 6.3). Further the frequency distribution of the diastolic blood pressure appears to be fairly symmetrical both in 1950 and in 1951-52. A selection of the material on the basis of a stratification of the systolic blood pressure did

not lead to any essential skew in the distribution of the diastolic blood pressure (see Figs. 6.9 and 6.10). In none of these distribution curves of the systolic or diastolic blood pressure or of the difference between the 1950 and 1951-52 recordings is there any evidence of bimodality. This holds for the high as well as the low blood pressure groups in all ages in both sexes.

However it must be emphasised that the groups with the highest blood pressure (> 210 mm systolic) consist of so few individuals, especially men, that no definite conclusions can be drawn. This deficiency of the series could be reduced by making adjustments for difference in age over the whole range of the age distribution as suggested by Hamilton *et al.* (90). It would therefore be of interest to apply a similar technique to this series and present the distribution curves in each of the 4 blood pressure strata.

Another explanation of the bimodality of the distribution curves presented by Platt (183) and Morrison & Morris (158) is the possibility of technical errors in using the conventional sphygmomanometer owing to differences between observers in their measurement technique.

The possibility of an unconscious tendency to over-record certain figures and to avoid borderline readings, e.g. 140/90 or 150/100 has been suggested by Pickering and his group and several others. Therefore the new blood pressure apparatus developed by the London School of Hygiene (100) will be of particular interest. This apparatus has been shown to diminish digit preference. In the present study however all readings are taken by one observer (the author) and the blood pressure has been recorded to the nearest 5 or 0 (see p. 67). Although there is a definite tendency to record 0 more frequently than 5 there is no evidence of bimodality in the blood pressure distributions (using a class interval of 10 mm Hg).

Secondly when relating the cardiac findings to blood pressure, there is some



evidence of a linear relationship between the blood pressure (systolic and diastolic) and the different cardiac signs. This is seen when estimating the size of the heart physically by palpating the apex beat (displaced apex beat, see Fig 7 11) The more objective methods of estimating the heart size, using the electrocardiographic criteria of left ventricular hypertrophy or estimating the relative heart volume radiologically also illustrate this linear relationship. Furthermore, the auscultatory findings, including apical and aortic systolic murmurs (see Figs. 7 15 and 7 16) and accentuation of the second aortic sound (see Fig 7 17) show an even increase with blood pressure.

These findings seem to support Pickering's hypothesis that there is a quantitative relationship between blood pressure and cardiac findings and that blood pressure behaves as a graded characteristic.

Besides this relationship there is also a definite linear relationship between age and the same cardiac findings. In some of the findings the influence of age seems to be greater than that of blood pressure. This is clearly seen from the analyses of the frequency of the symptom dyspnoea and of coronary heart disease. The radiological estimation of the size of the heart also shows a definite effect of age. The regression lines show a linear increase with age in both sexes which is somewhat greater than the effect of blood pressure (see Table 8 7).

In the physical estimation of the heart size by recording the displaced apex beat 10 cm or more from midsternal line (see Figs. 7 11 and 7 12) and in some of the auscultatory findings there is an even increase with age in the low blood pressure groups ( $\leq 100$  mm Hg diastolic, see apical systolic murmur Fig 7 15 and accentuated aortic second sound, Fig 7 17) while in the high blood pressure group ( $\geq 105$  mm Hg diastolic) this effect of age is partly abolished. The same pattern is also seen when analysing the frequency of electrocardiographic signs of

cardiac enlargement on systolic classification of the series. There is, however one exception to this pattern aortic systolic murmurs in men with low blood pressure ( $\leq 85$  mm diastolic or  $\leq 145$  mm systolic) do not show any increase with age, in contrast to the findings in all the other blood pressure groups in both sexes (see Fig 7 16). However these murmurs occur so infrequently in the low blood pressure groups that one cannot draw any definite conclusions from these data.

In other words the cardiac signs and symptoms are influenced by age and blood pressure an interplay which seems to be of great importance in the natural course of hypertensive disease.

As mentioned above the frequency of several cardiac findings is lower in the oldest age groups with high blood pressure than in the preceding age groups. This is seen when analysing the frequency of displaced apex beat (Fig 7 12) and accentuated second aortic sound (Fig 7 17) in both sexes. Coronary heart disease also shows the same. In men the frequency of the electrocardiographic signs of left ventricular hypertrophy (Figs. 7 18 & 7 19) and of the relative heart volume also decreases in the oldest age group with high blood pressure.

It has been suggested that these findings could be due to an effect of excess mortality. High blood pressure increases the load on the heart and the height of the blood pressure is considered to be a factor in the production of hypertensive heart failure and premature death.

The findings in this series seem to be in conformity with this concept however they are not conclusive, as the findings can also be explained by differences in the attendance rates among the groups. A more detailed review and discussion of this lack of completeness in the series has been given in chapter V p. 58.

Several follow-up studies have shown a worse prognosis in hypertensive men. The electrocardiographic findings and the radiologically estimated heart size seem

to be compatible with the above reservations.

The third main question is whether this study can give any contribution to clinicians dealing with cases of high blood pressure. While the clinician deals with cases, the epidemiologist deals with groups of individuals, and this study is based upon a subsample of the population of Bergen (including the well and the sick and those with high and low blood pressure) suitable for quantitative comparisons.

Therefore one must be very careful in relating the findings to single cases. This study gives very little contribution to the knowledge of the individual. The findings only supplement the clinical picture. According to Morris (154) such epidemiological studies help to complete the clinical picture and natural history of disease. Moreover this investigation, as described in chapters VII and VIII, presents the results from the reduced series, e. g. the series with high blood pressure without evident cause. Therefore no conclusion can be drawn regarding cases with secondary hypertension either. However in chapter VI it is shown that a small group of 5 women, aged 30-39 (composed of 3 cases of renal disease, 1 in the malignant phase of essential hypertension and 1 with diabetes) show blood pressure findings which deviate from the findings of all the other groups in the same blood pressure stratum (see p. 112). The other groups are larger and composed of only solitary cases of secondary hypertension, and the blood pressure in these cases does not deviate from that in the others in any way. Thus, this small example illustrates that when a group consists mainly of special cases, the findings deviate from the general trend and it is only in view of all the other groups that this phenomenon could be recognized.

Finally, what experience has the work on this study given to the author, a cardiologist, starting the study as an amateur in the field of epidemiology?

The first conclusion is that it is of para-

mount importance to pay attention to the technique of interviews and the methods of examination in surveys of this type.

In planning the questionnaire (see p. 46) the author decided not to use a too detailed subgrouping of all symptoms and signs, as all the interviews and examinations were to be carried out by the same investigator. It was essential that the diagnostic criteria should be clear and capable of classifying the individuals into groups with symptoms and signs of varying severity. In chapter VII examples of the criteria for all cardiac symptoms and signs are given. In grading the symptom dyspnoea, only two categories, slight and marked, were found to be appropriate (see p. 121). However it would have been of great value to have included a quantitative test (a simple spirometer test) to get more precise comparisons.

In interviewing the individuals on symptoms indicating coronary disease the technique of questioning was based on the criteria given on p. 138. The author did not use such detailed standardized questioning as that presented by Rose (197) in the recently developed English version of a cardiovascular questionnaire. The necessity for uniformity with regard to criteria and definitions of symptoms and signs is important, so that comparable studies can be made. The technique of using a standard form of symptomatic questionnaire has been developed since this survey was started. The objects of the technique are to record answers that represent the facts as closely as possible and to avoid bias due to different techniques of questioning. Although the author has asked all the questions, error or bias by cross-examination cannot be avoided.

Furthermore, the investigator has not tried to measure the repeatability and the observer error and observer variations in all the different qualitative and quantitative tests. It is certainly of importance to estimate the magnitude and frequency of the variability. In chapter VI (p. 67)

comments on the accuracy of the blood pressure readings are given and in chapter VIII (p. 200) the observer variation in reading the X rays has been presented otherwise no tests on the observer variability in estimating the heart size clinically or on the auscultatory findings over the heart have been performed.

Next, it is of importance not to start a survey of this type without careful consideration beforehand as to the usefulness of the primary series from which the sample is drawn.

At the time of planning one had only a slight idea of the representativeness of the primary series. It was decided, however from the very beginning that the main object was to obtain a series covering all grades of blood pressure capable of answering the hypothesis to be tested. Furthermore it was considered of importance to reinvestigate the blood pressure of the selected series as soon as possible after the mass radiography and blood pressure measurements in group I.

Therefore insufficient emphasis was laid upon the exact representativeness of the primary series at that stage of the planning. An account of this crucial point is given in chapter III p. 32 and it is concluded that the lapse rate is so great that the series must be deemed selective. The attendance varied in the different age groups and this again could lead to fallacious inferences.

The conclusion is therefore that surveys, even compulsory of the whole population, with lapse rates as in the Bergen series, are not reliable if the main object is to draw general conclusions.

Furthermore, when a written request was sent to people randomly selected from the primary series, explaining the purpose of the study and asking them to attend voluntarily for a thorough investigation, no further approach was made to influence those who did not attend except the sending of another letter of request (see p. 46).

It is regrettable that one did not try

relentlessly to get in touch with these people. Informative propaganda should be arranged, either by nurses visiting the homes and working places, or through the local press, asking them to attend the survey.

To see the people in their homes or working places was impossible because of the rather complicated examinations including electrocardiograms and radiological examinations of the heart.

The need for obtaining a nearly 100 per cent response should be remembered in surveys of this type, but according to Fletcher & Oldham (72) the most relentless investigations have usually failed to obtain information from between 5 and 10 per cent of the group studied. As shown in chapter V the average lapse rate of the pathological groups of the study group was 17% in men and 21% in women, and in the group with blood pressure  $\leq 145$  mm Hg systolic the average lapse rate was 30% in both sexes.

Again, this subsample is taken from the primary series, which had an average lapse rate of 25% in men and 17% in women.

It is therefore unduly optimistic to assume that the findings and conclusions from this particular series will hold true for any group of the general population. According to Dorn (53) two conditions must be fulfilled if valid inferences are to be drawn from a sample. The sample must be representative of the population to which inferences are to be drawn and the data collected must be capable of answering the hypothesis to be tested or the questions to which answers are sought. In general, it cannot be said that one of these is more important than the other. In any practical problem, if a choice is necessary one may decide to give greater weight to the desirability of obtaining more reliable data with some consequent restriction in the generality of the population concerning which inferences can be drawn.

The findings in this selective series show a characteristic trend indicating a quanti-

tative, linear relationship between age and blood pressure and the different cardiac signs and symptoms.

Future studies should be encouraged to see whether new series, representative of

the general population, will verify the findings presented in this monograph. This study should, to some extent, be looked upon as a pilot study on this particular and important problem.

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SUPPLEMENTUM 408

## CALCIUM KINETICS IN OSTEOPENIA AND PARATHYROID DISEASE

by

JOHN FREDRIK DYMLING

*Accompanies Vol. 178*

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LUND 1964



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# I INTRODUCTION

In 1736 Belchier reported that when pigs were fed extracts of madder root their bones became red. With this communication Belchier pioneered tracer methodology progress in the field of bone physiology has ever since been intimately linked with progress in the use of tracers. On the basis of tracer experiments, the generations of John Hunter and Astley Cooper speculated on bone kinetics in man under normal and pathological conditions. Cooper (1824) emphasized the importance of metabolic bone disease in the etiology of fractures in the aged. He expressed the opinion that in the aged the skeleton loses bone because of a decrease in the rate of bone for

mation, whereas the rate of bone resorption stays nearly normal. This opinion was adopted more than a century later by Albright and provided a basis for his hypothesis on the etiology of osteoporosis (Albright and Reifenstein, 1948)

With the introduction of tracer methods for quantitation of bone kinetics in man, the stage was set for an objective evaluation of previous speculations. This communication reports the results of tracer studies in normal adults, osteopenic subjects with and without treatment with anabolic steroids, and subjects with parathyroid disease.

## II METHODS

### A. Terminology and definitions

Pommer (1885) introduced the terms osteomalacia and osteoporosis to distinguish between two major morbid conditions of the skeleton. Osteomalacia was defined as a condition with decreased mineralization associated with wide non mineralized osteoid seams. Osteoporosis was defined as a condition with decreased skeletal mass associated with increased porosity. Both conditions were thus defined on morphological grounds.

Later investigations showed osteomalacia in adults and rickets in children to be related to vitamin D metabolism and measurable alterations in mineral and enzyme metabolism. Today the diagnosis of osteomalacia is more often based upon biochemical criteria than morphology.

The biochemical basis of osteoporosis, on the other hand, is still unknown, and the definition and clinical diagnosis of osteoporosis is vague.

In Albright's classification of metabolic bone disease (Albright and Reifenstein, 1948) osteoporosis is defined on etiological grounds as a condition due to a decreased rate of bone matrix formation. This etiological concept

which was purely hypothetical became universally accepted. A word was needed to describe decreased bone density as visualized radiographically and many radiologists adopted the term osteoporosis. Realizing the difficulties involved in the objective evaluation of decreased bone density certain workers require demonstration of a vertebral fracture before they accept the diagnosis osteoporosis (Urist, 1960) — In summary osteoporosis may mean one of the following things

- 1 Decreased skeletal mass with increased porosity
- 2 Decreased skeletal mass due to deficient matrix formation.
- 3 Decreased density radiographically
- 4 Decreased density radiographically with normal serum concentration of calcium, phosphate, and alkaline phosphatase

This state of affairs is highly unsatisfactory and to solve these terminological difficulties Bauer, Carlsson, and Lindquist (1958) proposed the term osteopenia. Osteopenia is defined as too little calcified bone in the same sense as used by Albright. Osteopenia is a purely descriptive term in which all skeletal states with decreased den-

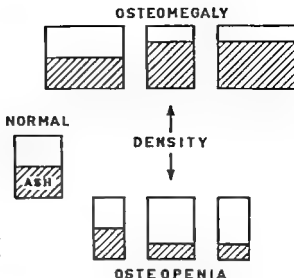


Figure 1. Metabolic bone disease classified according to density and ash content. For further explanations see text.

sity are included. It comprises a variety of bone diseases such as osteoporosis (in any meaning) osteomalacia rickets, and osteitis fibrosa, and does not by definition require radiographic visualization. On the other hand osteopenia is exactly what may be visualized radiographically.

Osteopenia can be divided into different categories according to certain parameters. One of these parameters is the degree of mineralization. Three states can be differentiated (Fig 1)

- 1 Decreased mass of organic tissue with normal mineral content. An example of this is osteitis fibrosa generalisata. The main group however is osteoporosis in Pommer's sense. This is probably a heterogeneous group of several diseases in which the axial skeleton in particular develops osteopenia with normal mineralization. In these cases the serum chemistry is normal

with regard to calcium, phosphate, and alkaline phosphatase. The pathogenesis is unknown.

- 2 Normal mass of organic tissue with decreased mineral content. By definition this is osteomalacia in adults or rickets in children.
- 3 Decreased mass of organic tissue with decreased mineral content. This is a combination of 1 and 2 above. As the skeletal mass and the skeletal volume (Frost, 1962) can not be estimated in vivo, at the present time it is impossible to differentiate this group from osteomalacia.

The opposite of osteopenia is logically osteomegaly. Theoretically three categories can be distinguished with regard to degree of mineralization (Fig 1). These are generally referred to as osteopetrosis or osteosclerosis.

*Standard statistical procedures have been applied*



## B Radiographic evaluation

The radiographic evaluation was based on radiographs of the dorsal and lumbar spine, pelvis, skull, hands, and femora. Since the loss of bone in idiopathic osteopenia, generalized osteopenia associated with rheumatic disease, or following gastric resection, has a marked predilection for the axial skeleton (Albright and Reifenshtein, 1948; McConkey, Fraser and Bligh, 1962; and Lutwak and Whedon, 1963) the radiographs of the spine were regarded as the main point at issue. It has been demonstrated, that a vertebral body may lose twenty five to fifty per cent of its mineral content before this loss can be visualized radiographically (Lachman and Whelan, 1936; Babiantz, 1947; Fust, 1953; and Fraser, 1957). This is a severe limitation of technique, which at present cannot be readily overcome.

For the purpose of this study the following features were recorded in the evaluation of radiographs of the spine:

1. Decreased density of the vertebral bodies.
2. Accentuation of the endplates of the vertebral bodies.
3. Accentuation of vertical trabeculae of the vertebral bodies.
4. Compression fractures of the vertebral bodies.
5. Increased height of the intervertebral discs.

In Tables I—VI positive findings have been marked with +. Patients with less than three plus were not accepted as osteopenia.

## C Chemical determinations

Serum calcium was determined with Eppendorf's flame photometer.  
Normal mean 5.0 mEq per liter  
Normal limits 4.5—5.5 mEq per liter

Serum phosphate was determined as inorganic phosphate soluble in acid according to Chen, Toribara and Warner (1956).

Normal mean 3.6 mg per 100 ml.  
Normal limits 2.4—4.7 mg per 100 ml.

Alkaline phosphatase was determined according to The Sigma Technical Bulletin (1957).

Normal mean 4 units.  
Normal limits 2—8 units.

## D Tracer data

Carrier free  $\text{Ca}^{45}$  (half life 4.9 days) or  $\text{Sr}^{90}$  (half life 65 days) were used.

The isotope was given as a single, rapid, intravenous injection of a high specific activity. The amount of calcium or strontium given did not exceed 0.3 mg or 0.003 mg respectively. The contamination of  $\text{Ca}^{45}$  in the  $\text{Ca}$  batches did not exceed two per cent. Following isotope administration the serum, urine, and faecal activities were determined for twelve days (Wendeborg, 1964). External counting (Bauer and Wendeborg, 1959) was performed over the knees, thighs, and spine, usually after 24, 168, and 336 hours. The maximal dose administered was 1  $\mu\text{C}$  per kilogram body weight or 50  $\mu\text{C}$ . The amount of radiation delivered to the skeleton by this dose was cal-

culated to be less than the maximal permissible dose recommended by the International Commission on Radiological Protection (Bauer and Wendenberg 1959)

When calcium tracers are injected into the vascular space, they are diluted in the body fluids and picked up by the skeleton into one comparatively small exchangeable fraction and incorporated into the non-exchangeable skeletal calcium, the major fraction of skeletal calcium. The rate of incorporation into the non-exchangeable fraction—the accretion rate—can be calculated provided the tracer does not return from this fraction during the investigation period.

The various kinetic parameters can be calculated in several ways. In 1955 Bauer, Carlsson and Lindquist derived an equation for the accretion rate. Heaney and Whedon (1958) independently proposed a way to calculate the same parameter. Bauer and Ray (1958) proposed a four-compartment model, which was modified to an open two-compartment model by Wendenberg (1961 and 1962). Later other types of calculations have been proposed. These have recently been reviewed by Heaney (1963).

In this study an open two-compartment model drained by excretion and accretion has been used for the kinetic analysis (Wendenberg, 1961, 1962, and 1964). The first compartment ( $S_1$ ) is rapidly exchangeable and principally located in the body fluids. An approximate value for the size of this compartment can be calculated from the dilution at one hour. At this time al-

most complete mixing has been attained within the compartment and the loss of activity by accretion, excretion, and exchange with the second compartment ( $S_2$ ) is small. Compartment  $S_2$  exchanges more slowly and reaches equilibrium in three to four days. When the specific activities in compartment  $S_1$  and  $S_2$  are equal a moment of transient equilibrium is reached. At this time the total amount of exchangeable calcium ( $S = S_1 + S_2$ ) can be calculated. Knowing  $S_1$ ,  $S_2$  can be calculated. The moment of transient equilibrium has been found to occur between twelve and thirty six hours after injection (Wendenberg 1964). In this study it was routinely regarded as twenty four hours.

The accretion rate was calculated from the five and ten day values using the equation of Bauer, Carlsson, and Lindquist (1958). The excretory clearance rates were calculated directly. The calculated values do not differ appreciably from values calculated with other methods (Dymling, 1964).

The symbols adopted are those proposed by Sheppard (1962). These symbols differ somewhat from those used earlier in this laboratory but it was regarded as advantageous to adopt a common system of symbols in tracer work. The symbols are as follows:

- |            |  |
|------------|--|
| $S$        | total amount of exchangeable calcium.              |
| $S_1, S_2$ | total amounts of calcium in compartments I and II. |
| $a_1, a_2$ | specific activities in compartments I and II.      |
| $k_a$      | accretion rate.                                    |

|       |                                   |
|-------|-----------------------------------|
| $k_u$ | urinary clearance rate.           |
| $k_r$ | endogenous faecal clearance rate. |
| $t_i$ | time of injection of tracer       |
| $t$   | time from $t_i$ .                 |
| Ret   | total body retention.             |

Rates are expressed as liters of plasma cleared per day and compartment sizes are denoted as liters of plasma to permit a uniform terminology when bone tracers other than the calcium isotopes were used, e.g.  $Sr^{90}$ . Provided that the calcium concentration in the serum is five milliequivalents per liter ten liters of plasma contain one gram of cal

cium. Consequently the figures for rates and compartment sizes in the normocalcemic patients in this study may be converted to grams of calcium by dividing with a factor of ten.

The excretory mechanisms of strontium differ from those of calcium, but accretion rates and compartment sizes are comparable, when tracer doses are used (Eisenberg and Gordan 1961). This is illustrated by case C-149 in Table IV where a simultaneous study with Ca and  $Sr^{90}$  was performed. Other studies not included in this series have yielded similar results.

### III NORMAL MATERIAL

#### A. Clinical material

It was difficult to gather a material of "normal persons, because the investigation period was inconveniently long, and because hospitalization was required to collect urine and faeces. Therefore, investigations classed as normal were performed in patients with minor old or inactive orthopaedic diseases patients with fractures sustained shortly before or several months prior to the investigation and patients with nephrolithiasis without clinical evidence of hyperparathyroidism.

The criteria for normality were as follows

- 1 Absence of generalized disease
- 2 Absence of osteopenia radiographically
3. Normal serum concentrations of calcium, phosphate and alkaline phosphatase.
- 4 Age over twenty five years.
- 5 Normal external counting except over localized bone lesions.

The age limit was chosen because children and adolescents differ from adults in their calcium kinetics. External counting was performed in order to rule out cases with altered ki-

netics in a considerable part of the skeleton.

Using these criteria twenty four investigations were made eleven with  $\text{Ca}^{45}$  and thirteen with  $\text{Sr}^{90}$  (Table 1) Four cases were completely normal. Eight cases were hospitalized because of solitary renal calculus. Four cases had sustained fractures, one of the metatarsals and three of the tibia. The tibial fractures were twenty six (B-83) fifty two (C-13) and one (D-35) months old. One patient had osteoarthritis of the hip (coxarthrosis) one had a prolapsed intervertebral disc, and one had slight trauma to the back without radiographic evidence of fracture. Also included were one case of Scheuer mann's disease, two cases of bone infection, and two cases of inactive skeletal tuberculosis. — The mean age was forty four years with a range from twenty five to sixty-eight.

#### B Results

The results are shown in Tables 1 and I Although the number of cases was limited, there was no significant difference between investigations carried out with  $\text{Ca}^{45}$  and  $\text{Sr}^{90}$  The mean

TABLE 1 *Results of kinetic studies in twenty four normal cases*

*Rates are given in liters of plasma cleared per day and compartment sizes in liters of plasma*

| Normal cases | No. | Mean | S.D. |
|--------------|-----|------|------|
| $k_1$        | 24  | 4.49 | 1.01 |
| $S_1$        | 24  | 22.0 | 4.5  |
| $S_{II}$     | 24  | 23.8 | 7.9  |
| $k_{Ca}$     | 18  | 7.0  | 3.7  |
| $k_{Sr}$     | 11  | 2.3  | 0.9  |
| $k_{Ca}$     | 13  | 2.6  | 1.1  |
| $k_{Ca}$     | 11  | 1.9  | 0.6  |

accretion rate in the eleven cases studied with  $Ca^{45}$  was 4.31 and in the thirteen cases studied with  $Sr^{90}$  4.64. Nor was there any consistent difference with age. The mean accretion rates in different age groups (decades from twenty five to seventy five years) were 4.56 4.81 3.34 5.07 and 4.13. A comparison between the largest group the cases of renal lithiasis, and the rest gave accretion rates of 4.47 and 4.50 respectively.

## C Discussion

The results of the kinetic analyses in this group show a wide variation. One standard deviation was roughly twenty to thirty per cent of the mean in the case of accretion rates and exchangeable compartments. This may be due to one or more of the following causes, (1) lack of precision of the method, (2) variations in skeletal mass, or (3) variations in turnover rates for unknown reasons. These will be discussed in turn.

1 The radioactivity in samples was invariably measured with pulse height analysis and all values with less than five per cent accuracy were rejected. In the cases where several investigations have been performed without known environmental changes the kinetic data agreed remarkably well. This is demonstrated by cases A 21 B-44 and D-40 in Table II case C-133 in Table IV and cases HB and HR in Bauer Carlsson, and Lindquist (1958). In these six patients a total of eighteen investigations were performed demonstrating the consistency in consecutive studies.

2 Variations in skeletal mass are important. By definition the accretion rate is a rate constant related to the turnover of the skeletal mass. This means that the larger the skeletal mass, the higher will be the normal accretion rate and vice versa. Elsenberg and Gordan (1961) have shown that athletes have a higher accretion rate than normal persons not indulging in athletics. This may be attributed to a larger skeletal mass of the athletes, since it is widely accepted that heavy muscular work leads to an increase in skeletal mass (Albright and Reifenstein, 1948).

3 Variations in the skeletal turnover may be caused by unknown endogenous and exogenous factors. It is to be expected that normal variations in calcium homeostasis due to alimentary hormonal, and perhaps other factors, may alter calcium kinetics.

Heaney has collected thirty radiocalcium studies in persons classed as nor-

imals from different laboratories (Heaney et al., 1964) Cases B-86 C-75 D 12, E-41 and E 108 were included In this joint study When the same calculation as used here was applied, the accretion rate was 3.59 liters of plasma per day the exchangeable compartments 20.4 liters of plasma ( $S_i$ ) and 19.2 liters of plasma ( $S_u$ ) and the urinary and faecal clearance rate 1.4 liters of plasma cleared per day These figures are lower than in the studies presented here. No explanation can be offered for this difference.

## D Conclusions

The mean accretion rate was 4.49 liters of plasma cleared per day with a standard deviation of 1.01 The sizes of compartment  $S_i$  and  $S_u$  were 22.0 and 23.8 liters of plasma with standard deviations of 4.5 and 7.9 respectively The urinary clearance rate of calcium was 2.2 and of strontium 7.0 liters of plasma per day and the faecal clearance rate of calcium 1.9 and of strontium 2.6 liters of plasma per day

## IV OSTEOPENIA

### A. Clinical material

The subjects were chosen among patients attending Malmö General Hospital with a complaint of backache, and a diagnosis of osteopenia based on radiographic evaluation. Presence of at least three of the five criteria of vertebral bone loss was required. Furthermore, a normal serum concentration of calcium, phosphate, and alkaline phosphatase was required. Patients with osteogenesis imperfecta or signs of generalized disease except as specified below were excluded. The subjects were divided into (1) idiopathic osteopenia (2) osteopenia associated with rheumatic disease, and (3) osteopenia following gastric resection.

#### 1 Idiopathic osteopenia

Thirty four investigations were made in twenty nine patients. Two patients were investigated three times and one patient twice. Between investigations these patients received no treatment, and no known environmental change occurred.

The mean age was sixty-one years with a range from thirty-one to seventy-eight years. There were nine males and twenty females. Pertinent

data are found in Table II including radiographic evaluation. Vertebral fractures were present in nineteen of the twenty nine patients.

#### 2 Osteopenia associated with rheumatic disease

Osteopenia is commonly seen in association with rheumatic disease. The reason for separation of this group was the suggestion, that the rheumatic process affects the bone collagen (McConkey Fraser and Bligh, 1962)

Ten investigations were made in two males and eight females with a mean age of fifty seven years and a range from thirty nine to seventy three years. Cases D-67 and E-95 were on treatment with corticosteroids.

#### 3 Osteopenia following gastric resection

The reason for separation of this group was the possibility that gastric resection causes malabsorption of calcium and/or vitamin D. This is easily detected in many gastrectomized patients (Nicolaysen and Ragård, 1955 and Hall and Neale, 1963). In the group studied here there were no obvious signs of malabsorption, such as steatorrhea, abnormal concentrations of iron and vitamin B<sub>12</sub> in the serum, or

abnormal values of Schilling's and the glucose tolerance tests. Electrophoretals of the serum proteins showed normal values for the albumin fraction and an inconsistent slight increase in the  $\alpha_1$ -globulin fraction, but no abnormal lies in the other globulin fractions.

Fourteen investigations were made in eleven males and one female with a mean age of fifty five years and a range from thirty-eight to sixty seven years. In one case, C-149 a simultaneous investigation with  $\text{Ca}^{45}$  and  $\text{Sr}^{90}$  was performed.

## B Results

The results are shown in Tables 2 and II III and IV and Figures 2 3 and 4. The accretion rate was significantly lower ( $p < 0.001$ ) than normal in the cases with idiopathic osteopenia. The size of compartment  $S_2$  was probably significantly lower ( $0.05 > p > 0.01$ ) than normal in rheumatic osteopenia. All other differences from the normal material were statistically non significant ( $p > 0.05$ ).

## C Discussion

The results showed that in idiopathic osteopenia the excretory clearance rates of calcium and strontium were normal, and the exchangeable calcium and strontium spaces were normal or decreased. The accretion rate showed a decrease of sixteen per cent in the rheumatic cases ( $p > 0.05$ ) and twenty seven per cent in the idiopathic cases ( $p < 0.001$ ). Although there is no way of estimating skeletal mass in pathological cases, it can be postulated that when osteopenia can be diagnosed radiographically the loss of skeletal mass exceeds twenty five per cent (page 8). Consequently the accretion rates per unit bone were probably not decreased in any of the groups of osteopenia studied here. It seems likely at least in the group of osteopenia following gastric resection, that they were increased.

In the group of idiopathic osteopenia there were four cases with an accretion rate below two liters of plasma cleared per day and in the group of rheumatic osteopenia one such case. It may be

TABLE 2 Results of fifty seven kinetic studies in fifty-one osteopenic cases. Rates are given in liters of plasma cleared per day and compartment sizes in liters of plasma.

|                  | Osteopenia idiopathic |      |      | Osteopenia rheumatic |      |      | Osteopenia post gastric resection |      |      |
|------------------|-----------------------|------|------|----------------------|------|------|-----------------------------------|------|------|
|                  | No.                   | Mean | S.D. | No.                  | Mean | S.D. | No.                               | Mean | S.D. |
| k                | 34                    | 3.25 | 1.06 | 10                   | 3.76 | 1.33 | 13                                | 4.63 | 1.66 |
| $S_1$            | 34                    | 22.3 | 4.5  | 10                   | 23.1 | 4.4  | 13                                | 24.7 | 4.8  |
| $S_{II}$         | 34                    | 20.6 | 4.8  | 10                   | 17.7 | 5.2  | 13                                | 25.8 | 4.3  |
| $k_1 \text{ Sr}$ | 21                    | 6.1  | 1.7  | 7                    | 6.8  | 2.2  | 12                                | 3.9  | 2.4  |
| $k_1 \text{ Ca}$ | 13                    | 7.1  | 1.5  | 3                    | 2.0  | —    | 2                                 | 0.7  | —    |
| $k_2 \text{ Sr}$ | 21                    | 2.3  | 0.5  | 7                    | 2.5  | 1.2  | 12                                | 2.7  | 0.4  |
| $k_2 \text{ Ca}$ | 13                    | 1.6  | 0.6  | 3                    | 1.8  | —    | 2                                 | 1.8  | —    |



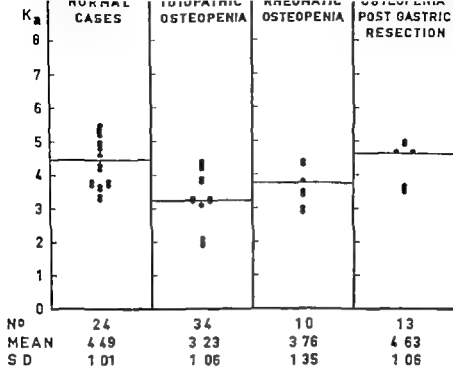


Figure 2. Accretion rates in liters of plasma cleared per day in normal cases and osteopenia.

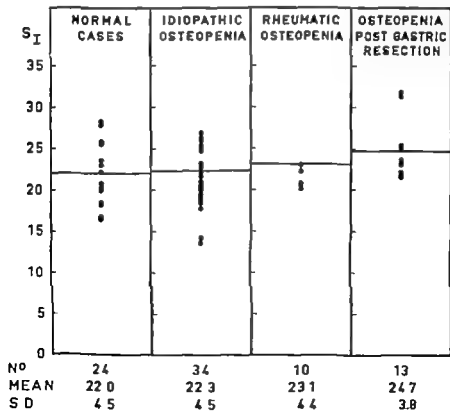


Figure 3. Compartment  $S_1$  in liters of plasma, in normal cases and osteopenia.

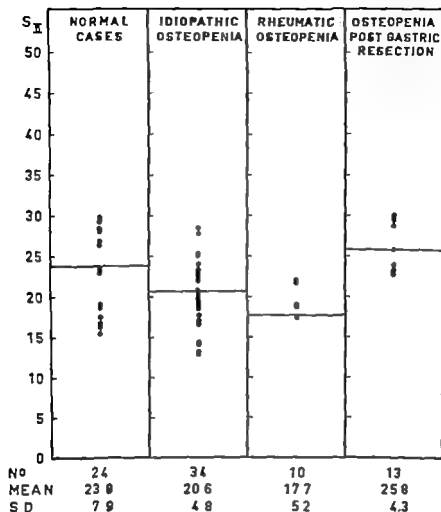


Figure 4. Compartment  $S_{II}$  in liters of plasma, in normal cases and osteopenia.

possible that in cases with such low accretion rates, even the accretion rate per unit bone may be decreased. These may represent a specific group of osteopenia. Clinically they did not show any specific features.

Heaney and Whedon (1958) reported normal BFR ("bone formation rate") in four cases of idiopathic osteo-

penia and two cases of rheumatic osteopenia. The exchangeable pool ( $S$ ) seemed to be decreased in the rheumatic cases and possibly in two of the idiopathic cases. Heaney (1962) reported increased accretion rates in osteopenia of disuse. Dow and Stanbury (1960) reported two cases with idiopathic osteopenia. In three simultane-

ous  $\text{Ca}^{45}$  and  $\text{Sr}^{90}$  studies on these patients body retention and compartment sizes were found to be within normal limits. Nordin reported seven cases of idiopathic osteopenia studied with  $\text{Ca}^{45}$  in 1959 and Nordin, Mac Gregor and Bluhm reported twelve cases studied with  $\text{Sr}^{90}$  in 1963. They found normal or increased accretion rates, and in the 1959 series normal exchangeable pools. Rich, Ensick, and Fellows (1961) reported thirteen cases of osteopenia studied with continuous infusion of  $\text{Ca}^{45}$  and one case studied with continuous infusion of  $\text{Sr}^{90}$ . The amount of miscible calcium was increased in eight studies, within normal limits in eleven and decreased in two.

Eisenberg and Gordan (1961) reported forty studies in twenty six cases of unequivocal osteoporosis and Fraser, Harrison, and Ibbertson (1960) reported twenty-one cases of osteopenia.

In these investigations a stable strontium technique was used. Eisenberg and Gordan found significantly reduced exchangeable pools and "bone deposition rates." Fraser, Harrison and Ibbertson on the other hand found values within the normal limits in twenty cases. Their twenty first case had low values but was complicated with hypoparathyroidism.

Most of these investigations agreed well with the results presented here.

## D Conclusions

Tracer studies in idiopathic and rheumatic osteopenia and osteopenia following gastric resection have shown that the accretion rates per unit bone were rarely lower than normal and not infrequently higher.

# V OSTEOPENIA DURING TREATMENT WITH ANABOLIC STEROIDS

## A Clinical material

The clinical material consisted of nine cases of idiopathic osteopenia, two cases of osteopenia following gastric resection and one case of systemic lupus erythematosus. The last case was on chronic medication with corticosteroids, but did not fulfill the radiographic criteria for osteopenia (only two plus). After an initial tracer investigation treatment was started with anabolic steroids. In ten cases 19-nortestosterone phenyl propionate was given in dosage of twenty five milligrams weekly. In cases D-65 and D-30 19-nortestosterone-decanoate was given in a dosage of twenty five milligrams every third week. A second investigation was made six to twenty two months after treatment was started, while the patients were on medication.

## B Results

The results are shown in Tables 3 and 4 and Figure 5. During treatment with anabolic steroids the exchangeable

spaces and the excretory clearance rates remained constant. The accretion rate increased in one case of osteopenia following gastric resection (C-133) but decreased in the other (C-149). In two slender women (D-65 and D-90) the accretion rates increased during treatment and in two women with considerable overweight (D-25 and D-73) it decreased. On the whole the accretion rates increased or decreased without apparent consistency during treatment with these anabolic steroids.

Cases C-133 and D-30 noted no subjective change during treatment, whereas all of the others noted relief of pain and a general sense of well being. All eight females developed some hirsutism. The degree of hirsutism was not enough to cause any apparent psychologic problems. In case D-40 there was slight and in case D-96 a marked change in voice towards a low and coarse pitch. This change of voice persisted even three years after medication was discontinued.

Changes in heights of the intervertebral discs were noted in five cases. In cases D-25, D-73 and D-90 the heights of the intervertebral discs decreased and in cases D-61 and D-65 they in-

Duraboline® and Deca Duraboline® was generously supplied by V. V. Organon (Netherlands) through Pharmacia, Sweden.

TABLE 3 Results of twenty four kinetic studies in twelve patients before and during treatment with anabolic steroids. Rates are given in liters of plasma cleared per day and compartment sizes in liters of plasma

| Case No         | Duration of treatment | k         |         | S <sub>1</sub> |         | S <sub>2</sub> |         | k <sub>10</sub> |         | k <sub>1</sub> |         | k <sub>2</sub> |         | k <sub>3</sub> |         |
|-----------------|-----------------------|-----------|---------|----------------|---------|----------------|---------|-----------------|---------|----------------|---------|----------------|---------|----------------|---------|
|                 |                       | Untreated | Treated | Untreated      | Treated | Untreated      | Treated | Untreated       | Treated | Untreated      | Treated | Untreated      | Treated | Untreated      | Treated |
| B-44            | 7                     | 3.06      | 2.80    | 26.4           | 26.1    | 18.6           | 22.1    | 5.9             | 7.3     | 3.1            | 2.3     | 3.1            | 2.3     | 3.1            | 2.3     |
| C-133           | 11                    | 2.69      | 4.27    | 21.6           | 26.8    | 32.8           | 23.2    | 2.8             | 2.6     | 2.4            | 1.5     | 2.4            | 1.5     | 2.4            | 1.5     |
| C-149           | 0                     | 5.99      | 4.53    | 26.4           | 26.0    | 31.1           | 34.3    | 0.6             | 0.0     | 2.1            | 2.4     | 2.1            | 2.4     | 2.1            | 2.4     |
| D-25            | 14                    | 5.72      | 3.97    | 29.2           | 27.4    | 25.2           | 25.8    | 7.7             | 8.6     | 2.3            | 2.3     | 2.3            | 2.3     | 2.3            | 2.3     |
| D-31            | 15                    | 3.06      | 3.03    | 22.2           | 24.4    | 17.1           | 19.2    | 4.0             | 2.9     | 1.1            | 1.3     | 1.1            | 1.3     | 1.1            | 1.3     |
| D-40            | 7                     | 3.50      | 2.47    | 12.6           | 16.6    | 26.2           | 24.0    | 6.2             | 6.2     | 1.9            | 2.6     | 1.9            | 2.6     | 1.9            | 2.6     |
| D-43            | 23                    | 3.36      | 2.49    | 23.0           | 31.8    | 22.6           | 26.4    | 6.2             | 6.5     | 2.7            | 3.4     | 2.7            | 3.4     | 2.7            | 3.4     |
| D-61            | 6                     | 2.37      | 1.88    | 25.0           | 26.3    | 25.2           | 20.0    | 1.3             | 2.3     | 1.5            | 2.0     | 1.5            | 2.0     | 1.5            | 2.0     |
| D-63            | 16                    | 2.08      | 4.59    | 17.8           | 16.6    | 11.8           | 16.0    | 7.0             | 1.6     | 3.1            | 1.4     | 3.1            | 1.4     | 3.1            | 1.4     |
| D-73            | 0                     | 5.53      | 2.40    | 25.0           | 22.5    | 22.0           | 22.4    | 2.0             | 1.2     | 0.1            | 0.8     | 0.1            | 0.8     | 0.1            | 0.8     |
| D-96            | 6                     | 1.74      | 3.06    | 14.2           | 18.7    | 16.7           | 14.6    | 1.1             | 1.0     | 1.6            | 2.0     | 1.6            | 2.0     | 1.6            | 2.0     |
| Additional case |                       |           |         |                |         |                |         |                 |         |                |         |                |         |                |         |
| D-36            | 12                    | 2.16      | 2.09    | 15.8           | 16.9    | 16.0           | 14.7    | 4.5             | 6.7     | 2.0            | 2.1     | 2.0            | 2.1     | 2.0            | 2.1     |
| Mean            |                       | 3.53      | 3.36    | 21.7           | 23.5    | 21.3           | 21.1    |                 |         |                |         |                |         |                |         |

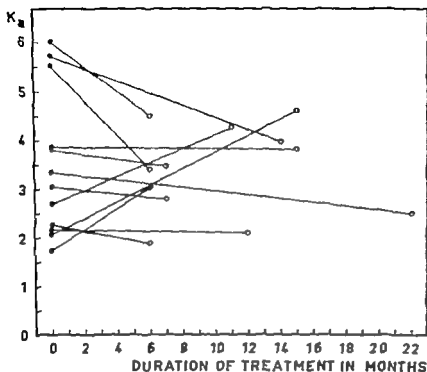


Figure 8. Accretion rates in liters of plasma cleared per day before and during treatment with anabolic steroids.

creased. The significance of this finding is uncertain.

### C. Discussion

According to the theory postulated by Albright testosterone and other so called anabolic steroids should be effective in the treatment of idiopathic osteopenia (Albright and Reifenstein, 1948; Reifenstein, 1957). This has not been verified clinically and no well established case has been reported in which idiopathic osteopenia has improved radiographically. Treatment with anabolic agents in cases of idio-

pathic osteopenia can induce a positive nitrogen balance (Kochakian 1946) and retention of calcium or a decreased loss of calcium (Nowakowski 1962). During long term treatment it appears that this effect fades off and a prolonged positive nitrogen or calcium balance cannot be maintained (Dymling, Isaksson, and Sjögren 1962; Isaksson and Sjögren, 1963).

The balance technique gives only a net balance between anabolism and catabolism. The effects of anabolic steroids on the accretion rate reported here, were inconsistent. This may be explained by either of two possibilities

- 1 There is no consistent effect of these anabolic steroids in idiopathic osteopenia
- 2 There are effects in certain cases, which are included in the heterogeneous group of osteopenia. However at the moment these cases cannot be clinically recognized.

## D Conclusions

Accretion rates were not consistently improved by long term treatment with 10 nortestosterone phenyl propionate or 10 nortestosterone-decanoate.

## VI PARATHYROID DISEASE

### A. Clinical material

The clinical material consisted of twelve cases of primary hyperparathyroidism, one case of hyperparathyroidism secondary to renal disease, two cases of hypoparathyroidism, and one case of nephrocalcinosis (additonal case) (Table VI). Case histories are given below in chronological order.

**Case 4-4** Male, born in 1907. Two brothers have been treated surgically because of duodenal ulcer. In 1925 he was treated for gonorrhea with epididymitis. In 1940 a gastric resection was performed because of duodenal ulcer. In 1951 he presented with an acute pyelonephritis. Nephrocalcinosis was discovered. Radiographically this could be traced back to 1948. The nephrocalcinosis showed a slight progression between 1951 and 1957 but has since remained constant. Skeletal radiographs showed a decreased density but no other abnormalities. He was never azotemic, and the serum creatinine was always within normal limits in spite of severe attacks of acute pyelonephritis. Defective function of the renal tubules with isosthenuria has been observed since 1951. The serum calcium was generally within normal limits but since 1951 occasional samples demonstrated hypercalcemia. A considerable number (15) of hypercalcemic crises were found through the years. The serum phosphorus was generally within normal limits but with low values. The alkaline phosphatase

was normal, with occasional elevated values. After a tracer study had been performed he was operated upon in November 1962, and three parathyroids were removed from normal localizations (Surgeon A. Wenckert, M.D.). The size and histology of these parathyroids were normal. Tracer studies were repeated seven days and seven months postoperatively. Serum calcium determinations were within normal limits postoperatively.

*Comment:* Clinical evidence supported a diagnosis of primary hyperparathyroidism, which could not be positively verified histologically.

**Case 8-63** Female, born in 1908. In 1950 she was hospitalized twice and in 1958 once because of duodenal ulcer. Recurrent attacks of upper right abdominal pain since the late thirties led to the detection of gallbladder stones in 1956. Recurrent attacks of renal colic since 1952. Pyelolithotomy was performed on the left side in March 1957. The stone constituents were calcium and carbonate. At that time hypercalcemia was noted and in September 1957 the neck was explored. A left subtotal thyroidectomy was performed and a thyroid adenoma was removed on the right side. No parathyroid adenoma was found. The hypercalcemia persisted, nephrolithiasis recurred and in March 1958 another exploration of the neck was performed. Several adenomatous structures were removed, no parathyroid adenoma was found. At this stage the alkaline phosphatase was increased and hypercalcemia persisted. There were no skeletal abnor-



malities visible radiographically. After a tracer study had been performed the neck was explored a third time and a parathyroid adenoma of chief cell type was found on the left side low down between the trachea and the recurrent nerve (Surgeon  $\square$  Jönsson, M.D.) The serum calcium, serum phosphate and alkaline phosphatase returned to normal, and remained normal three months after operation, when she was reinvestigated.

*Comment* Primary hyperparathyroidism.

*Case B-82* Male, born in 1906. He sustained a trauma to the left kidney in 1941. In 1953 a calculus was removed from the left kidney. In 1955 a nephrectomy was performed on the left side because of pyonephrosis. In March 1958 he developed acute abdominal pain, anuria, and azotemia. A calculus was removed, which blocked the passage from the right pelvis to the ureter. A coralliform calculus developed postoperatively and at this stage hypercalcemia was found. After complementary investigations had been performed a parathyroid adenoma was removed, located intracapsularly in the left upper lobe of the thyroid (Surgeon G. Jönsson, M.D.) Histological diagnosis: adenoma of mixed cell type, predominantly chief cells. The serum calcium returned to normal after operation.

*Comment* Primary hyperparathyroidism.

*Case C-4* Female, born in 1906. Apart from gynecological troubles, which terminated in hysterectomy in 1956, she was perfectly fit until 1950, when an ureterolithotomy was performed on the right side. She subsequently had no renal trouble until 1958, when she was hospitalized because of bilateral nephrolithiasis. Hypercalcemia and hypophosphatemia was found. She was referred for complementary investigations and the neck was explored in January 1959. A parathyroid adenoma of mixed cell type was found low down in the thoracic inlet on the left side (Surgeon G. Jönsson, M.D.) Serum calcium, serum phosphate returned to nor-

mal and remained normal ten months after operation when she was reinvestigated.

*Comment* Primary hyperparathyroidism.

*Case C-59* Female, born in 1917. In 1948 nephrolithiasis on the left side, hypercalcemia and decreased serum phosphate was discovered. In 1952 a normal parathyroid was removed together with a small thyroid adenoma. Hypercalcemia persisted. In 1954 she was hospitalized with the same findings of moderate hypercalcemia, nephrolithiasis, and normal skeletal radiographs. In 1955 she suffered from increasing lassitude and the hypercalcemia was more marked. In 1956 the neck and mediastinum were explored and a subtotal thyroidectomy performed. Intracapsularly in the thyroid one normal parathyroid was found. There was no effect on the hypercalcemia. In 1959 she was reinvestigated. There was hypercalcemia, bilateral calcifications in the kidneys, hypertension, no azotemia, but creatinine clearance reduced to 20 ml per minute. No skeletal changes were visible radiographically. After a tracer study one enlarged parathyroid was removed, located low on the left side close to the oesophagus (Surgeon G. Jönsson, M.D.) Histological diagnosis: predominantly chief cells, probably adenoma. The differential diagnosis versus hyperplasia was difficult because no portion of the normal parathyroid could be demonstrated on the margin of the tumour. Postoperatively the serum calcium became normal.

*Comment* Primary hyperparathyroidism.

*Case C-150* Female, born in 1914. In 1954 a small tumour was removed from the left mandible. The tumour recurred and in 1956 a biopsy showed a benign giant-cell tumour. She received radiotherapy and was operated. Osteitis fibrosa was questioned by the pathologist. In 1958 another benign giant-cell tumour was excised from the right maxilla, and in 1959 a biopsy was taken from a tumour in the right part of the frontal bone. Again the pathologist suspected osteitis fibrosa. This was now evaluated and verified. There were no cal-

cifications in the kidneys. Serum calcium and alkaline phosphatase were elevated and serum phosphate low. A tracer study was performed in March 1960. At operation a large parathyroid adenoma of chief cell type was removed, located below and behind the right lobe of the thyroid (Surgeon G Jönsson, M.D.). Postoperatively the serum calcium fell to hypocalcemic values and she was treated with vitamin D for a year during which time the skeletal lesions healed.

*Comment:* Primary hyperparathyroidism with osteitis fibrosa generalisata.

*Case D-56* Male, born in 1901. In 1950 ureterolithotomy was performed on the right side. In 1951 he had nephrolithiasis on the right side and one serum calcium value was 5.7 milliequivalents per liter. In 1958 he suffered from renal colic on the right side and in 1959 on the left side. At that time he was hospitalized, a silent kidney was found on the right side with masses of calcifications in the renal pelvis. No calculus was found on the left side. Serum calcium was elevated, but the patient refused operation and was discharged. — In 1960 he was treated for *lupus erythematosus discoides*. At that time he had developed pain from his right kidney. Nephrectomy was performed on the right side. Hypercalcemia persisted and the parathyroid function was evaluated. In September 1960 two large parathyroids were removed, located caudally on the right and left side behind the recurrent nerve (Surgeon T Widen, M.D.). Histologically general hyperplasia of water-clear cell type. Postoperatively serum calcium and serum phosphate were within normal limits.

*Comment:* Primary hyperparathyroidism.

*Case E 116* Male, born in 1924. In 1948 he had an acute attack of left sided renal colic but normal pyelogram. In 1953 he had another attack of left sided renal colic. No stones were visible radiographically. In 1961 he slowly developed lassitude, thirst, and lost weight. In September

he had a new attack of left sided renal colic. Calcifications were found in the left renal pelvis. He was hospitalized, hypercalcemia and decreased serum phosphate was found. After a tracer study he was operated in October 1961. Two enlarged parathyroids were removed and the histological diagnosis was general hyperplasia of water-clear cell type. No effect on the hypercalcemia. Reoperated in February 1962, when a tumour weighing seven grams was removed, located behind the upper part of the right thyroid (Surgeon A. Wenckert, M.D.). Histological diagnosis: general hyperplasia of water-clear cell type. The serum calcium and serum phosphate became normal.

*Comment:* Primary hyperparathyroidism.

*Case E 120* Female, born in 1906. In 1950 hysterectomy was performed. In 1951 cholecystectomy was performed and she had an acute pyelitis with calculi. No serious trouble until 1961 when the pyelogram showed bilateral nephrolithiasis and left sided ureterolithiasis. At that time hypercalcemia was discovered. A ureterolithotomy was performed. Her calcium metabolism was evaluated, a tracer study performed and in October 1962 she was explored and a parathyroid adenoma of water-clear cell type was removed, located at the right caudal position (Surgeon T Widen, M.D.). Postoperatively serum calcium and serum phosphate became normal.

*Comment:* Primary hyperparathyroidism.

*Case E 130* Female born in 1919. There was a history of chronic pyelonephritis starting in 1940. In 1952 she had an endogenous creatinine clearance of 21 ml per minute. In 1955 she had a non-protein nitrogen of 59 mg per 100 ml and hyposthenuria. At that time the serum calcium and phosphate were normal. Her renal disease progressed and in November 1960 she has had a non-protein nitrogen varying between 90 and 115 mg per 100 ml, a slight acidosis, and serum phosphate between 6.0 and 7.0 mg per 100 ml. The serum cal

clum has remained normal. In the summer of 1960 she developed pains in the back and thighs. These progressed and head ache was added. She was hospitalized in November 1961 and radiographic changes were found in the skeleton suggesting secondary hyperparathyroidism (Plate I and II). She had amino-aciduria with slightly increased concentrations of serine, tyrosine, and glutamic acid. She was treated with AT 10 ("dihydroxycholesterol") and the pain rapidly vanished. In four months the skeletal changes had returned to normal. *Comment* Hyperparathyroidism secondary to longstanding chronic pyelonephritis. Excellent effect of treatment with AT 10.

*Case F-88* Female, born in 1912. She was treated surgically for thyrotoxicosis in 1943. Postoperatively she had latent tetany and treatment with AT 10 ("dihydroxycholesterol") was started. For unknown reasons this was maintained less than a year. In June 1962 she was hospitalized and gave a history of latent tetany and monthly tetanic seizures over more than ten years. She had severe hypocalcemia but no cataracts and no intracranial calcifications. The skeleton was generally denser than normal radiographically suggesting osteomegaly. *Comment* Hypoparathyroidism after thyroidectomy.

*Case F-89* Male, born in 1922. In 1960 he had his first attack of nephrolithiasis. A solitary calculus passed spontaneously. Hypercalcemia was registered but unnoticed. In February 1962 he had a second attack and a calculus was removed from the left ureter. He had still hypercalcemia. The calcium metabolism was evaluated, and a tracer study was performed. In October 1962 the neck was explored and two enlarged parathyroids located close to the inferior thyroid artery were removed (Surgeon I. Sandberg, M.D.). Histological diagnosis: general hyperplasia of water-clear cell type. The serum calcium and phosphate returned to normal after parathyroidectomy. *Comment* Primary hyperparathyroidism.

*Case F-120* Female, born in 1896. In 1941 she suffered from duodenal ulcer. In January 1962 she had arrhythmic fibrillation and cardiac decompensation. She was extremely sensitive to digitalis. In July 1962 she was hospitalized for cholecystitis and hypercalcemia was accidentally discovered. This proved to be intermittent. The serum phosphate was low normal. Radiographically there was decreased density of the skeleton but no calcification in the kidneys. In December 1963 she was explored and a parathyroid adenoma of chief cell type was removed from the right caudal position (Surgeon H. Ryd, M.D.). The serum calcium fell to normal values immediately postoperatively.

*Comment* Primary hyperparathyroidism without clinical symptoms, discovered accidentally.

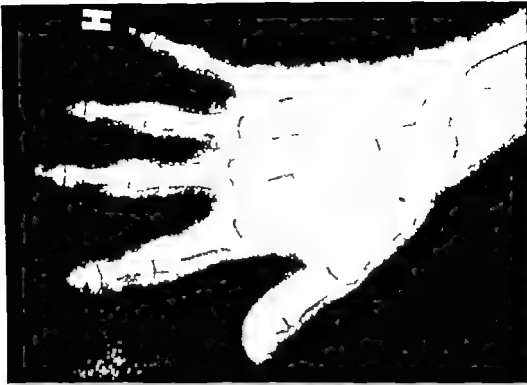
*Case G-14* Male, born in 1911. He had no previous history. In January 1963 he sustained a fracture through a cystic tumour in the left radius. The histological diagnosis was osteitis fibrosa. Radiographically there was generalized osteitis fibrosa. He was severely hypercalcemic. There were no renal calculi and no nephrocalcinosis but the non-protein nitrogen was slightly elevated. In February a large parathyroid adenoma was removed, located close to the inferior thyroid artery between the right lobe of the thyroid and the oesophagus (Surgeon A. Wenckert, M.D.). Histological diagnosis: parathyroid adenoma consisting of practically only oxyphilic cells. Postoperatively the serum calcium and the non-protein nitrogen returned to normal and the osteitis fibrosa showed radiographic signs of healing.

*Comment* Primary hyperparathyroidism with osteitis fibrosa generalisata. Of special interest was the histological finding of an oxyphilic adenoma.

*Case G-116* Female, born in 1938. She had her first attack of renal colic in February 1963. On the pyelogram there was one calculus in each kidney. The right-sided calculus passed spontaneously. In October



Fig. 1. Profile radiograph of the L. II of case L. 120 before and after 4 months treatment with VT 10.



Plat II R elograph of the right ha d f caso E 130 bef re and after f ur m the treatment ith VT 10

1963 she had another attack of renal colic and four calculi were discovered in the left kidney one in the right kidney and one in the right ureter. She had hypercalcemia and hypophosphatemia. After evaluation and tracer study a parathyroid adenoma was removed, located close to the inferior thyroid artery on the right side (Surgeon H. Rvd, M.D.). Histological diagnosis: parathyroid adenoma, mainly chief cells. Postoperatively serum calcium returned to normal within three days.

*Comment:* Primary hyperparathyroidism.

*Case G-126:* Female born in 1905. No previous history. In June 1962 a subtotal thyroidectomy was performed because of mul-

tiple adenomas. Postoperatively the serum calcium fell to hypocalcemic values. She was treated with calcium supplements but progressively developed symptoms characteristic of hypoparathyroidism. No vitamin D treatment was given before the tracer study. Calcium supplement therapy was stopped three days prior to the injection of tracer.

*Comment:* Hypoparathyroidism after thyroidectomy.

## II Results

The results are shown in Figures 6 - 8 and Tables 4 and V.

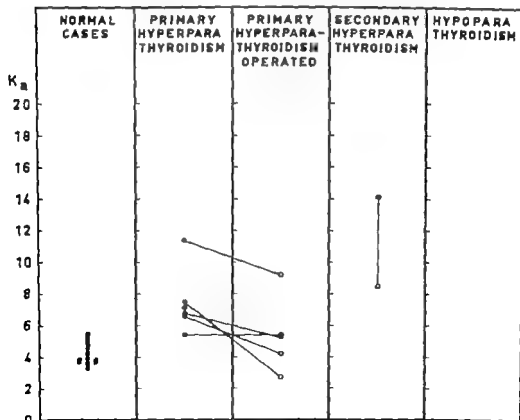


Figure 6. Accretion rates in liters of plasma cleared per day in normal cases and parathyroid diseases.

eral years standing the accretion rate was extremely low. The exchangeable compartments were below the normal mean but within the normal limits. The excretory clearance rates were within the normal limits.

## C Discussion

### *1 Primary hyperparathyroidism*

In earlier series there are reports of seven patients with primary hyperparathyroidism studied with radiocalcium or radiostrontium (Krane, Brownell, Stanbury and Corrigan 1956, Van Dilla and Arnold, 1956, Rich, 1957, Dow and Stanbury 1960, Rich, Ensinnck, and Fellows 1961, Bauer Carlsson, and Lindquist, 1961). In addition nine patients published by Fraser Harrison, and Ibbertson in 1960 and twenty-eight published by Eisenberg and Gordan (1961) were studied with stable strontium.

Dow and Stanbury reported normal bone turnover in one patient. This patient had no clinical evidence of bone disease but coexistent diabetes mellitus and myocardial infarction may have influenced the kinetic study. Rich studied one case of osteitis fibrosa generalisata before and after partial parathyroidectomy for hyperplasia. The accretion rate was very high before operation and decreased postoperatively. Rich, Ensinnck, and Fellows studied three patients with hyperparathyroidism without evidence of osteitis fibrosa generalisata with the continuous infusion technique. The miscible pool was elevated in two cases and at the upper limit of normal in the third.

Bauer Carlsson and Lindquist calculated accretion rates in two cases studied by van Dilla and Arnold, and Krane, Brownell, Stanbury and Corrigan respectively. In both cases the accretion rates were increased and in one of them the total exchangeable compartment (S) was increased.

In the series of nine patients reported by Fraser Harrison, and Ibbertson, all showed increased rates of bone turnover and seven showed an increased exchangeable calcium mass. Only two in this series had no evidence of bone disease. After operation the avidity for calcium in the bones persisted. In Eisenberg and Gordan's series a correlation between bone involvement on one hand and increased pool size and bone deposition rate on the other was postulated. Where no radiographic or histological evidence of bone disease was detected the exchangeable pool sizes were normal and the bone deposition rates tended to be low. Both of these parameters tended to increase with increasing degree of bone involvement.

The results presented do not give a clear-cut picture. There are data supporting the concept of increased bone turnover even in the absence of radiographically apparent bone disease in the seven patients reported by Rich, Ensinnck, and Fellows, Bauer Carlsson, and Lindquist, and Fraser Harrison, and Ibbertson. Eisenberg and Gordan on the other hand suggested that the results were dependent on the degree of bone involvement. In contradiction to this Smeenk (1961) using a phosphate exchange technique on bone

specimens *in vitro* claimed that in hyperparathyroidism the skeleton was always involved. According to the hypothesis of Smeenk, osteitis fibrosa generalisata develops when the bone metabolism in hyperparathyroidism becomes decompensated.

The data in this series showed that *a* the highest accretion rates were found in cases of osteitis fibrosa generalisata. In this respect the findings of Eisenberg and Gordan were supported.

*b* the majority of cases had an increased accretion rate indicating bone involvement.

*c* the exchangeable spaces tended to be larger than the normal means but were only occasionally above the limit of two standard deviations. At shorter time intervals postoperatively they were sometimes increased, which corresponds to what Fraser Harrison and Ibbertson call the calcium avidity of bone.

*d* from the kinetic point of view there was no difference between parathyroid hyperplasia and adenoma.

## 2 Additional case

This man exhibited clinical signs of primary hyperparathyroidism. In the absence of azotemia and acidosis, renal disease with secondary hyperparathyroidism could be ruled out. After removal of three parathyroids, perfectly normal in size and histology he was observed for one year. The intermittent hypercalcemia seemed to have disappeared. Before operation he had a very markedly elevated accretion rate and the size of compartment S<sub>II</sub>

TABLE 1 Results of thirteen kinetic studies before and after operation in five patients with proven hyperparathyroidism and one normal control case. Rates are given in liters of plasma cleared per day and compartment sizes in liters of plasma.

| Case No.         | Lungs             |                   | S <sub>I</sub> |         | S <sub>II</sub> |         | S <sub>III</sub> |         | S <sub>IV</sub> |         | S <sub>V</sub> |         | Ad. Illness case |
|------------------|-------------------|-------------------|----------------|---------|-----------------|---------|------------------|---------|-----------------|---------|----------------|---------|------------------|
|                  | Preop.            | Postop.           | Preop.         | Postop. | Preop.          | Postop. | Preop.           | Postop. | Preop.          | Postop. | Preop.         | Postop. |                  |
| 1119             | 5.4 <sup>10</sup> | 5.4 <sup>10</sup> | 23.8           | 20.0    | 22.0            | 27.0    | 5.8              | 6.0     | 3.5             | 2.8     |                |         |                  |
| 11               | 5.4 <sup>10</sup> | 5.4 <sup>10</sup> | 26.6           | 23.3    | 20.2            | 21.0    | 11.1             | 3.2     | 1.8             | 2.8     |                |         |                  |
| 12-24            | 5.4 <sup>10</sup> | 5.4 <sup>10</sup> | 21.7           | 27.8    | 30.0            | 27.0    | 7.1              | 1.8     | 3.0             | 2.1     |                |         |                  |
| 1116             | 5.4 <sup>10</sup> | 5.4 <sup>10</sup> | 28.6           | 26.2    | 32.0            | 40.1    | 12.0             | 4.1     | 2.1             | 2.1     |                |         |                  |
| 111              | 5.4 <sup>10</sup> | 5.4 <sup>10</sup> | 20.8           | 27.1    | 32.4            | 38.7    | 2.8              | 0.2     | 1.1             | 0.8     |                |         |                  |
| Ad. Illness case |                   |                   |                |         |                 |         |                  |         |                 |         |                |         |                  |
| 11               | 5.4 <sup>10</sup> | 5.4 <sup>10</sup> | 11.07          | 1.15    | 30.8            | 31.2    | 1.7              | 5.0     | 3.1             | 2.8     |                |         |                  |
|                  | 5.4 <sup>10</sup> | 5.4 <sup>10</sup> |                | 3.11    | 28.2            | 28.2    |                  | 1.1     |                 | 1.7     |                |         |                  |



was above normal limits. Both these parameters returned to normal immediately after operation and remained so. The discrepancy between the clinical and histological findings cannot be explained.

**3 Secondary hyperparathyroidism**

No tracer study of secondary hyperparathyroidism has been reported earlier. It is interesting to note the remarkably high accretion rate, and the increase in the size of compartment  $S_1$ . Both these parameters were reduced considerably during medication with AT 10 which confirms the importance of this therapy (Albright and Reifstein, 1948; Dent, Harper and Philpot, 1961).

**4 Hypoparathyroidism**

Krane, Brownell, Stanbury and Corrigan (1958) and Heaney and Whedon (1958) each reported one case of untreated stable hypoparathyroidism without concomitant disease. In both cases the accretion rate was low. Rich,

Enslnck, and Fellows (1961) reported two cases with small miscible pools. Bell, Bartter and Smith (1963) reported two cases with low accretion rates and small miscible pools. Two cases with identical findings are added here. It seems unquestionable that untreated hypoparathyroidism has a low accretion rate.

**D Conclusions**

The hypoparathyroid state has a decreased accretion rate and the hyperparathyroid state has in the majority of cases an increased accretion rate. Kinetic studies in hyperparathyroidism give added information about the patient, which may be of importance in the differential diagnosis and in the evaluation of treatment.

*Addendum* In Case G 14 another study with  $Ca^{45}$  was performed ten months after operation. The following kinetic values were obtained  $k_a$  4.93  $S_1$  22.2  $S_2$  29.9  $k_e$  1.1 and  $k_f$  1.5

## VII. GENERAL DISCUSSION

In his classification of metabolic bone disease, Albright, on logical grounds, distinguished two causes of osteopenia "bone formation too little (osteoporosis and osteomalacia) and "bone resorption too much (osteitis fibrosa generalisata) (Albright and Reifstein, 1948). His views on osteitis fibrosa generalisata and osteomalacia were based upon findings that were histological, biochemical, and radiographic. Osteoporosis was not associated with evidence for either increased bone resorption or decreased mineralization, and on these grounds it was assumed that this condition was caused by a decreased rate of bone matrix formation. As no direct evidence is available to support this assumption, in this context it is unnecessary to discuss the further classification of causes of the alleged abnormality: postmenopausal osteoporosis due to defects in osteoblasts senile osteoporosis due to defects in matrix and idiopathic osteoporosis due to unknown defects, none of which have been verified experimentally.

The association of certain types of osteoporosis with hormonal imbalance and the rationale of hormonal treatment (Albright and Reifstein, 1948

and Reifstein, 1957) were based upon the observations (a) that osteoporosis was more common in women than in men and more serious after artificial menopause (b) that sex hormones had a profound influence on skeletal metabolism in mice and pigeons, and (c) that medication with sex hormones relieved pain and corrected the negative calcium and nitrogen balance seen in osteoporosis.

Albright conceded that it was difficult to produce undisputed evidence that the bones (excluding fracture sites) as visualized by x ray had become more dense following hormone therapy. Unfortunately methods for in vivo measurements in man of bone mass (radiography) were imprecise, and of bone formation rate were not yet available. Radiographic methods for in vivo measurements of bone mass are still imprecise, and the very diagnosis of too little calcified bone (osteopenia) can be made only in advanced cases.

The introduction of tracers of bone constituents has made it possible to estimate the rate of bone formation. The tracers used in this investigation,  $\text{Ca}^{45}$  and  $\text{Sr}^{90}$  are incorporated into the

skeleton both by formation of bone salt and by exchange with bone salt. The rate of bone salt formation can be calculated with precision if the relative importance of the exchange reaction can be determined. Opinion is divided regarding the importance of this reaction. At one extreme Nordin, Mac Gregor and Bluhm (1963) felt that the method of calculation used in this study overestimates the rate of bone salt formation, and at the other Bauer (1964) pointed out, that they will tend to underestimate the rate of bone salt formation in conditions with high skeletal metabolic rates. There seems to be unanimous agreement, however that sources of error in measurement of the rate of bone salt formation are sufficiently small not to influence the validity of comparisons of the accretion rate between different skeletal conditions.

The rate of bone salt formation does not necessarily reflect the rate of bone formation. In healing osteomalacia mineralization proceeds at a faster rate than does formation of bone matrix. When the mineral content of the skeleton is normal, however the rate of bone salt formation is directly proportional to the rate of bone tissue formation. The accretion rate of calcium or strontium measured with tracers would consequently be directly proportional to the rate of bone formation.

In this study it was found that the accretion rate in idiopathic osteopenia was lower than normal by one fourth. By definition the skeletal mass in these patients was decreased by one

fourth or more. It was concluded that the rate of bone formation per unit bone in idiopathic osteopenia was within the normal range.

Albright's general view on bone kinetics need not be immediately discarded. Tracer studies have demonstrated that the rate of bone formation is higher than normal in a number of conditions associated with localized bone loss fracture-induced osteopenia (Wendeborg 1961) osteopenia of disuse (Heaney 1962) and tumour rarefaction of bone (Corey et al., 1961 and Gynning Laugeland, Lindberg and Waldegaard, 1961). In these conditions it is reasonable to assume that the rate of bone formation has increased in response to an increased rate of resorption.

In this study it was found that the accretion rate was higher than normal in the majority of cases with hyperparathyroidism. The highest values were obtained in two cases of osteitis fibrosa generalisata. In hypoparathyroidism the accretion rate was found to be lower than normal. It is well known that a primary effect of parathyroid hormone is to increase bone resorption. Possibly the rate of bone formation in parathyroid disease varies in response to variations in the rate of bone resorption.

A normal rate of bone formation per se cannot account for the development of osteopenia and it seems reasonable to assume that the primary defect is one associated with increased bone resorption. Idiopathic osteopenia seems to be a condition in which the rate of bone formation fails to respond to the

needs of the skeleton. On this note, Albright's opinion may be upheld rather than contradicted by the results of tracer studies of skeletal metabolism.

It is unfortunate that the diagnosis of osteopenia can be made only in advanced cases. It is possible that if the diagnosis could be established at an earlier stage other kinetic relations would become apparent. For example, Wendeborg (1961) observed three stages of fracture induced osteopenia with the stage of high accretion rate preceded by a stage when it was normal and followed by a stage when it was below normal.

In the normal subjects studied, the observed range of accretion rates was found to be wide. The concept of normality as regards bone metabolism is, however, difficult to define. On this

score, tracer studies indicate that there is a need for increased precision in the measurement or evaluation of such parameters of bone metabolism as bone mass and bone morphology.

In the osteopenic subjects the range of accretion rates was also wide. It is not immediately clear what significance should be attached to the results of hormone treatment in the osteopenic subjects. In some the accretion rate increased, in some it decreased and in a majority of cases it stayed at pre-treatment levels. These findings may possibly be interpreted as evidence for subclinical differences between the subjects studied. The results showed that the effects of treatment with these agents will remain unpredictable until other methods permit a sharper differentiation of the various osteopenic conditions.

## VIII SUMMARY

### A. Methods

In a clinical series of ninety two cases the accretion rate and the exchangeable calcium or strontium pools were determined with the aid of  $\text{Ca}^{45}$  or  $\text{Sr}^{90}$ . The material was composed of twenty four normal subjects fifty-one cases of untreated osteopenia, eleven of whom and one additional case were studied before and during treatment with 19 nortestosterone-phenyl propionate and 10 nortestosterone-decanoate twelve cases of primary hyperparathyroidism, five of whom were studied both pre- and postoperatively one case of hyperparathyroidism secondary to renal disease, studied before and during treatment with AT 10 one case of nephrocalcinosis studied before and after partial parathyroidectomy and two cases of hypoparathyroidism. Following intravenous injection of the tracer serum and excreta collections were made for twelve days and analysed for tracer content.

### B Results

The results were expressed as pool sizes in units of liters of serum (ex-

changeable spaces) or clearance rates in units of liters of serum per day (accretion and excretion rates). The sizes of two exchangeable spaces were determined, one ( $\text{S}_1$ ) mainly associated with rapidly exchangeable mineral in the soft tissues and the other ( $\text{S}_2$ ) mainly associated with exchangeable bone mineral.

#### 1 Normals

The accretion rate was found to be  $4.49 \pm 1.01$ .  $\text{S}_1$  was  $22.0 \pm 4.5$  and  $\text{S}_2$   $23.8 \pm 7.9$ .

#### 2 Osteopenic subjects

Three groups of subjects were studied, those without apparent cause of the disease (Idiopathic osteopenia) osteopenia associated with rheumatic disease and osteopenia following gastric resection. In Idiopathic osteopenia the accretion rate was  $3.23 \pm 1.06$  in rheumatic osteopenia  $3.76 \pm 1.35$  and in osteopenia post gastric resection  $4.63 \pm 1.06$ . The value was significantly lower than normal in Idiopathic osteopenia. Values for  $\text{S}_1$  did not differ significantly from corresponding values in normals. The value for  $\text{S}_2$  was probably significantly lower than normal in rheumatic osteopenia.

Following treatment with anabolic steroids the accretion rates remained unchanged in six subjects, increased in three subjects and decreased in three subjects.

### 3 Parathyroid disease

Ten of the twelve cases with primary hyperparathyroidism had accretion rates higher than normal with highest values in the two cases who had signs of osteitis fibrosa generalisata. Following operation the accretion rate decreased in four out of five subjects. In one case of renal disease radiographic signs of secondary hyperparathyroidism disappeared during treatment with AT 10 and the accretion rate decreased from 14.13 to 8.51. Two cases of hypoparathyroidism had accretion rates of 1.57 and 0.75 respectively.

### C. Interpretation

The accretion rates in this series were interpreted as directly proportional to

the rate of bone formation. Inasmuch as the diagnosis osteopenia can be made radiographically only when the skeletal mass has decreased by one fourth or more, the similarly decreased accretion rates were interpreted as indicating a normal or even slightly higher than normal rate of bone formation per unit mass in the osteopenic subjects. The wide range of accretion rates in normals and osteopenic subjects and the inconsistent effect of hormone treatment on the accretion rate were interpreted to indicate subclinical differences between individuals.

### D. Conclusions

On the basis of comparisons with findings in certain specific types of osteopenia and in parathyroid disease it was concluded that the primary defect in osteopenia is associated with resorption rather than formation of bone and that the ability of bone formation to respond to loss of bone is decreased in idiopathic osteopenia.

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## XI TABLES

TABLE I. *Normal material*

|   |  |                  |                      |                           |             |
|---|--|------------------|----------------------|---------------------------|-------------|
| Cod No.                                 | B-6                                      | B-43             | B-65                 | B-86                      | 1           |
| Age (years)                             | 56                                       | 45               | 48                   | 52                        | 4           |
| Sex                                     | M  | M                | M                    | F                         | 1           |
| Occupation                              | War house-<br>worker                     | Seaman           | Musician             | Housewife                 | 1           |
| Weight (kg)                             | 50                                       | 64               | 68                   | 53                        | 1           |
| Radiography                             | -----                                    | -----            | -----                | -----                     | -           |
| Diagnosis                               | St. p. osteo-<br>myel. tbc.<br>fem. sin. | Sciatica         | Fract. tibiae<br>dx. | St. p. corit.<br>tbc. dx. | 1<br>1<br>1 |
| Isotope                                 | $\text{Ca}^{45}$                         | $\text{Sr}^{90}$ | $\text{Sr}^{90}$     | $\text{Ca}^{47}$          |             |
| $k_a$ (liters of plasma per day)        | 5.65                                     | 3.67             | 5.69                 | 3.75                      |             |
| $S_1$ (liters of plasma)                | 20.0                                     | 32.7             | 25.0                 | 16.7                      |             |
| $S_{\text{II}}$ (liters of plasma)      | 33.3                                     | 29.3             | 15.6                 | 16.6                      |             |
| $k_a$ (liters of plasma per day)        | 0.7                                      | 13.3             | 4.1                  | 1.1                       |             |
| $k_f$ (liters of plasma per day)        | 2.9                                      | 5.5              | 1.6                  | 1.1                       |             |
| $i$ (% dose per 10 l plasma)            |  |                  |                      |                           |             |
| $t = 1$ hour                            | 50.0                                     | 30.6             | 40.0                 | 60.0                      |             |
| 24 hours                                | 15.0                                     | 9.5              | 17.5                 | 24.0                      |             |
| 120                                     | 7.0                                      | 2.0              | 4.7                  | 9.0                       |             |
| 240                                     | 3.3                                      | 0.7              | 1.9                  | 5.0                       |             |
| $\int_0^t a_1$ (% dose per 10 l plasma) |  |                  |                      |                           |             |
| $t = 24$ hours                          | 17.5                                     | 17.5             | 26.0                 | 33.6                      |             |
| 120                                     | 56.5                                     | 33.1             | 63.2                 | 69.5                      |             |
| 240                                     | 81.7                                     | 41.5             | 78.1                 | 123.0                     |             |
| Ret (% dose)                            |  |                  |                      |                           |             |
| $t = 24$ hours                          | 89.8                                     | 65.5             | 85.7                 | 92.3                      |             |
| 120                                     | 90.8                                     | 32.5             | 63.4                 | 78.7                      |             |
| 240                                     | 89.4                                     | 22.5             | 55.5                 | 71.2                      |             |
| External counting<br>(% of standard)    |  |                  |                      |                           |             |
| Knee with lowest activity               |  |                  |                      |                           |             |
| $t = 24$ hours                          | 45.6                                     | 15.9             | 29.0                 | 53.0                      |             |
| 48                                      |  |                  | 24.0                 | 51.7                      |             |
| 168                                     | 33.8                                     | 6.4              | 14.1                 | 47.2                      |             |
| 336                                     | 25.4                                     | 6.0              | 9.2 (360 h)          | 33.7                      |             |
| Thigh with lowest activity              |  |                  |                      |                           |             |
| $t = 24$ hours                          | 25.8                                     | 6.7              | 11.1                 | 40.3                      |             |
| 48                                      |  |                  | 9.1                  | 36.4                      |             |
| 168                                     | 18.5                                     | 2.3              | 5.1                  | 30.9                      |             |
| 336                                     | 13.4                                     | 1.7              | 3.8 (360 h)          | 23.7                      |             |
| L IV                                    |  |                  |                      |                           |             |
| $t = 168$ hours                         |  |                  |                      | 67.7                      |             |
| 336                                     |  |                  |                      | 61.1                      |             |

TABLE I *Normal material*

|              | C-74                | C-75                | C-132               | D 12                | D-28                | D-35                |
|--------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|              | 55                  | 25                  | 28                  | 32                  | 42                  | 80                  |
|              | M                   | M                   | F                   | M                   | M                   | M                   |
|              | Floor<br>layer      | Farm<br>worker      | H usewif            | Electrician         | Mechanic            | Pipe-<br>layer      |
|              | 47                  | 60                  | 49                  | 78                  | 73                  | 61                  |
| Ex-<br>treme | Nephrol-<br>thiasis | Nephrol-<br>thiasis | Nephrol-<br>thiasis | Nephrol-<br>thiasis | Nephrol-<br>thiasis | Fract. tibia<br>dx. |
|              | Sr <sup>88</sup>    | Ca <sup>45</sup>    | Sr <sup>90</sup>    | Ca <sup>47</sup>    | Sr <sup>90</sup>    | Ca <sup>47</sup>    |
| 7            | 5.00                | 5.43                | 4.32                | 5.18                | 3.67                | 3.40                |
|              | 22.7                | 22.7                | 13.3                | 23.6                | 22.7                | 25.8                |
|              | 26.4                | 26.9                | 14.1                | 29.4                | 23.0                | 16.4                |
|              | 2.9                 | 2.9                 | 2.3                 | 3.1                 | 5.2                 | 2.4                 |
|              | 1.6                 | 1.7                 | 1.2                 | 1.9                 | 3.0                 | 2.1                 |
|              | 44.0                | 44.0                | 75.3                | 42.4                | 44.0                | 33.7                |
|              | 16.0                | 16.0                | 24.0                | 14.6                | 16.0                | 19.0                |
|              | 5.8                 | 6.2                 | 7.0                 | 6.1                 | 4.7                 | 8.0                 |
|              | 3.6                 | 3.2                 | 2.4                 | 2.6                 | 1.8                 | 3.8                 |
|              | 22.0                | 24.9                | 43.0                | 23.0                | 23.0                | 26.0                |
|              | 60.7                | 60.1                | 96.2                | 60.5                | 58.9                | 74.1                |
|              | 82.1                | 83.1                | 114.7               | 81.4                | 74.8                | 102.9               |
|              | 89.5                | 87.4                | 84.4                | 88.7                | 82.0                | 89.0                |
|              | 71.5                | 73.2                | 69.6                | 69.8                | 82.2                | 64.7                |
|              | 62.1                | 67.0                | 50.8                | 58.4                | 38.7                | 52.7                |
|              | 26.0                | 31.6                | 20.9                | 29.0                | 17.7                |                     |
|              |                     | 28.4                | 18.5                |                     | 18.5                |                     |
|              | 17.5                |                     | 12.8                | 21.1                | 10.5                |                     |
| 9 (288 h)    | 14.2 (288 h)        | 19.2 (312 h)        | 8.9 (312 h)         | 19.1 (210 h)        | 6.7                 |                     |
|              | 10.0                | 17.4                | 6.1                 | 17.7                | 7.1                 |                     |
|              |                     | 18.1                | 5.1                 |                     | 6.1                 |                     |
|              | 4.3                 |                     | 3.5                 | 11.9                | 4.0                 |                     |
| 6 (288 h)    | 5.2 (288 h)         | 11.2 (312 h)        | 2.9 (312 h)         | 10.9 (210 h)        | 3.0                 |                     |
|              | 43.8                |                     | 17.9                | 3.2                 |                     |                     |
|              | 47.9 (288 h)        | 49.6 (312 h)        | 16.8 (312 h)        |                     |                     |                     |

TABLE L. *Normal material*

|   |                     |                  |                  |                   |        |
|---|---------------------|------------------|------------------|-------------------|--------|
| Code No                                 | D-53                | D-76             | E 1              | E-41              |        |
| Age (years)                             | 47                  | 30               | 63               | 50                |        |
| Sex                                     | F                   | F                | F                | F                 |        |
| Occupation                              | Housewife           | Secretary        | Housewife        | Housewife         |        |
| Weight (kg)                             | 38                  | 58               | 56               | 58                |        |
| Radiography                             | -----               | -----            | -----            | -----             |        |
| Diagnosis                               | Fract.<br>metatars. | Nephrolithiasis  | Coxarthrosis     | Contusio<br>dorsi | M<br>m |
| Isotope                                 | Ca <sup>45</sup>    | Sr <sup>90</sup> | Sr <sup>90</sup> | Ca <sup>47</sup>  |        |
| $k_a$ (liters of plasma per day)        | 2.96                | 3.81             | 3.69             | 2.96              |        |
| $S_1$ (liters of plasma)                | 16.6                | 18.5             | 17.8             | 22.7              |        |
| $S_{11}$ (liters of plasma)             | 13.1                | 17.5             | 19.0             | 16.7              |        |
| $k_a$ (liters of plasma per day)        | 1.7                 | 6.1              | 9.7              | 1.5               |        |
| $k_f$ (liters of plasma per day)        | 1.5                 | 2.7              | 2.7              | 2.0               |        |
| $a_1$ (% dose per 10 l plasma)          |                     |                  |                  |                   |        |
| t = 1 hour                              | 60.3                | 54.1             | 36.0             | 44.0              |        |
| 24 hours                                | 26.5                | 18.0             | 18.0             | 20.2              |        |
| 120                                     | 9.4                 | 3.5              | 3.8              | 10.1              |        |
| 240                                     | 4.3                 | 0.9              | 0.9              | 8.2               |        |
| $\int_0^t a_1$ (% dose per 10 l plasma) |                     |                  |                  |                   |        |
| t = 24 hours                            | 40.0                | 32.0             | 24.4             | 26.4              |        |
| 120                                     | 99.3                | 65.9             | 49.8             | 84.0              |        |
| 240                                     | 131.8               | 75.5             | 58.5             | 121.2             |        |
| R t (% dose)                            |                     |                  |                  |                   |        |
| t = 24 hours                            | 90.7                | 77.1             | 69.8             | 87.3              |        |
| 120                                     | 68.2                | 44.8             | 37.7             | 66.5              |        |
| 240                                     | 56.7                | 23.8             | 27.6             | 50.3              |        |
| External counting<br>(% of standard)    |                     |                  |                  |                   |        |
| Knee with lowest activity               |                     |                  |                  |                   |        |
| t = 24 hours                            | 46.5                | 29.1             | 36.3             | 44.6              |        |
| 48                                      |                     | 21.8             | 30.2             |                   |        |
| 168                                     | 27.7                | 8.4              | 13.1             | 21.4              |        |
| 336                                     | 23.2                | 4.8              | 8.8              | 23.2              |        |
| Thigh with lowest activity              |                     |                  |                  |                   |        |
| t = 24 hours                            | 37.7                | 10.2             | 12.8             | 31.2              |        |
| 48                                      |                     | 6.4              | 10.7             |                   |        |
| 168                                     | 13.4                | 3.1              | 5.0              | 22.3              |        |
| 336                                     | 14.0                | 1.8              | 3.9              | 15.2              |        |
| L IV                                    |                     |                  |                  |                   |        |
| t = 168 hours                           | 53.7                | 12.5             |                  |                   |        |
| 336                                     | 46.6                | 9.2              |                  | 47.6              |        |

TABLE I *Normal material*

| OS               | F-10             | F-33                  | G-66                 | G-102            | G-103            | G-104            |
|------------------|------------------|-----------------------|----------------------|------------------|------------------|------------------|
| 53               | 30               | 28                    | 30                   | 33               | 32               |                  |
| F                | M                | M                     | M                    | M                | M                | M                |
| clergyman        | Saleslady        | Seaman                | Salesman             | Physician        | Physician        | Physician        |
| 49               | 65               | 67                    | 76                   | 0                | 65               |                  |
| phroli-<br>asis  | Normal           | Abscess,<br>fem. abn. | Nephroli-<br>thiasis | Normal           | Normal           | Normal           |
| Ca <sup>47</sup> | Sr <sup>90</sup> | Sr <sup>90</sup>      | Sr <sup>90</sup>     | Ca <sup>47</sup> | Ca <sup>47</sup> | Ca <sup>47</sup> |
| 4.78             | 4.31             | 5.53                  | 3.67                 | 3.34             | 3.92             | 4.07             |
| 0.8              | 20.3             | 25.7                  | 19.3                 | 14.6             | 18.4             | 20.2             |
| 3.5              | 19.1             | 48.2                  | 22.1                 | 18.8             | 29.8             | 29.1             |
| 1.6              | 7.3              | 12.6                  | 6.0                  | 3.1              | 3.3              | 3.1              |
| 1.1              | 2.3              | 3.6                   | 3.4                  | 1.8              | 1.6              | 2.8              |
| 8.0              | 49.3             | 39.0                  | 51.9                 | 68.4             | 34.2             | 33.4             |
| 7.0              | 16.0             | 8.4                   | 17.2                 | 24.8             | 16.5             | 14.2             |
| 8.8              | 3.               | 2.3                   | 4.8                  | 3.6              | 6.3              | 5.0              |
| 4.7              | 1.2              | 1.0                   | 1.7                  | 2.6              | 3.1              | 3.0              |
| 15.0             | 26.7             | 15.0                  | 27.5                 | 29.6             | 26.6             | 21.0             |
| 14.1             | 56.1             | 31.9                  | 64.4                 | 50.1             | 67.9             | 56.1             |
| 17.8             | 67.5             | 39.6                  | 69.0                 | 77.4             | 90.3             | 77.0             |
| 13.6             | 74.3             | 70.4                  | 81.3                 | 91.2             | 89.2             | 88.4             |
| 12.5             | 48.8             | 49.6                  | 48.1                 | 77.9             | 63.6             | 60.              |
| 4.1              | 36.6             | 32.4                  | 31.0                 | 61.7             | 56.0             | 54.6             |
|                  |                  | 24.6                  | 31.9                 |                  |                  | 64.1             |
|                  | 33.0             |                       | 25.3                 |                  |                  |                  |
| 61.1             | 15.4             | 12.4                  | 14.2                 | 23.1             | 21.5             | 49.6             |
| 50.4             | 12.0             | 7.9                   | 10.1                 | 14.6             | 12.3             | 30.8             |
|                  |                  | 8.9                   | 11.6                 |                  |                  | 23.4             |
|                  | 7.7              |                       | 9.7                  |                  |                  |                  |
| 30.9             | 4.0              | 3.3                   | 6.8                  | 13.8             | 17.0             | 13.0             |
| 26.7             | 8                | 2.1                   | 5.0                  | 8.8              | 9.1              | 17.3             |
| 01               | 1                | 1.6                   | 29.8                 |                  |                  | 91.1             |
| 03               | 13.6             | 13.0                  | 18.8                 | 33.6             | 61.1             | 70.1             |

TABLE II *Osteopenia idiopathica*

| Code No.                                  | A 21               | A 21             | A 21             | A 50                     |
|---|--------------------|------------------|------------------|--------------------------|
| Age (years)                               | 59                 | 62               | 64               | 51                       |
| Sex                                       | F                  | F                | F                | M                        |
| Occupation                                | School-<br>teacher |                  |                  | Gas<br>company<br>worker |
| Weight (kg)                               | 56                 | 56               | 56               | 4                        |
| Radiography                               | +++++              | +++++            | +++++            | + + - - +                |
| Isotope                                   | Str <sup>90</sup>  | Ca <sup>45</sup> | Ca <sup>45</sup> | Ca <sup>45</sup>         |
| k (liters of plasma per day)              | 1.44               | 2.20             | 2.68             | 3.74                     |
| S <sub>1</sub> (liters of plasma)         | 20.0               | 18.8             | 20.5             | 23.1                     |
| S <sub>0</sub> (liters of plasma)         | 22.2               | 13.3             | 1.7              | 25.3                     |
| k <sub>1</sub> (liters of plasma per day) | 9.1                | 2.5              | 3.9              | 2.1                      |
| k <sub>2</sub> (liters of plasma per day) | 2.9                | 1.4              | 1.4              | 2.1                      |
| a <sub>1</sub> (° dose per 10 l plasma)   |                    |                  |                  |                          |
| t = 1 hour                                | 50.0               | 33.5             | 48.9             | 39.9                     |
| 24 hours                                  | 15.3               | 22.5             | 19.7             | 16.0                     |
| 120                                       | 4.0                | 8.6              | .9               | 6.3                      |
| ∞   | 1.4                | 3.8              | 4.1              | 4.0                      |
| $\int_{t_0}^t$ (° dose per 10 l plasma)   |                    |                  |                  |                          |
| t = 4 hours                               | 25.0               | 32.0             | 31.3             | 22.0                     |
| 120                                       | 37.8               | 68.0             | 81.6             | 61.6                     |
| 40  | 69.6               | 115.5            | 111.2            | 87.0                     |
| Rel ° dos                                 |                    |                  |                  |                          |
| t = 4 hours                               | 69.0               | 85.0             | 83.7             | 63.8                     |
| 120                                       | 28.7               | 39.7             | 64.0             | 73.2                     |
| 40  | 16.0               | 44.0             | 51.7             | 64.0                     |
| External counting<br>° of standard)       |                    |                  |                  |                          |
| Knee with lowest activity                 |                    |                  |                  |                          |
| t = 4 hours                               | 4.8                | 69.3             | 111              | 29.5                     |
| 48  | 90.8               |                  |                  | 40.0                     |
| 168                                       | 10.1               | 43.5             | 68.5             | 29.7                     |
| 336                                       | 5.5 (312 h)        | 22.8             | 50.1             | 21.2                     |
| Thigh with lowest activity                |                    |                  |                  |                          |
| t = 4 hours                               | 12.1               | 40.4             | 66.7             | 22.0                     |
| 48  | 9.1                |                  |                  | 19.6                     |
| 168                                       | 4.7                | 37.0             | 35.8             | 14.1                     |
| 336                                       | 2.5 (312 h)        | 4.2              | 20.2             | 11.2                     |
| L IV                                      |                    |                  |                  |                          |
| t = 168 hours                             |                    | 48.1             | 122              |                          |
| 336                                       |                    | 18.9             | 105              |                          |

TABLE II. *Osteopenia idiopathica*

| B-44<br>66<br>M<br>Salesman | B-44<br>67<br>M  | B-44<br>68<br>M  | B-57<br>67<br>F<br>Single<br>woman | B-59<br>63<br>M<br>Composer | B-63<br>78<br>F<br>Housewife | C-3<br>49<br>F<br>Housewife |
|-----------------------------|------------------|------------------|------------------------------------|-----------------------------|------------------------------|-----------------------------|
| 85<br>+++++                 | 88<br>+++++      | 87<br>+++++      | 49<br>+++++                        | 71<br>+---++                | 56<br>+++++                  | 56<br>+++--+                |
| 5r <sup>26</sup>            | 5r <sup>26</sup> | 5r <sup>26</sup> | Ca <sup>27</sup>                   | Ca <sup>27</sup>            | Ca <sup>27</sup>             | 5r <sup>26</sup>            |
| 2.83                        | 3.26             | 3.05             | 3.98                               | 1.92                        | 4.16                         | 2.38                        |
| 23.4                        | 26.9             | 26.4             | 20.0                               | 33.1                        | 19.6                         | 18.6                        |
| 22.2                        | 20.6             | 18.6             | 14.4                               | 19.1                        | 13.2                         | 16.8                        |
| 8.6                         | 8.6              | 8.9              | 1.5                                | 5.9                         | 0.5                          | 4.6                         |
| 2.5                         | 2.8              | 3.1              | 1.1                                | 2.2                         | 0.8                          | 2.4                         |
| 39.4                        | 37.1             | 37.9             | 50.0                               | 30.2                        | 51.0                         | 54.0                        |
| 14.5                        | 15.0             | 15.0             | 22.5                               | 17.0                        | 21.5                         | 20.9                        |
| 3.9                         | 3.7              | 4.5              | 10.6                               | 10.0                        | 9.4                          | 6.3                         |
| 1.4                         | 1.2              | 1.9              | 4.7                                | 6.7                         | 5.5                          | 2.7                         |
| 21.0                        | 21.8             | 24.0             | 32.2                               | 22.0                        | 32.0                         | 37.0                        |
| 51.9                        | 51.5             | 56.7             | 112.0                              | 74.4                        | 89.8                         | 1.0                         |
| 64.3                        | 62.5             | 71.7             | 142.0                              | 116.0                       | 126.2                        | 91.7                        |
| 76.4                        | 75.2             | 75.1             | 86.9                               | 92.9                        | 93.7                         | 77.2                        |
| 43.4                        | 42.5             | 49.3             | 67.0                               | 77.2                        | 86.5                         | 46.0                        |
| 28.5                        | 28.7             | 35.4             | 36.0                               | 64.6                        | 62.4                         | 34.0                        |
| 12.5                        | 18.8             | 24.4             | 56.6                               | 49.4                        |                              | 23.0                        |
| 10.9                        |                  |                  |                                    |                             |                              | 21.8                        |
| 4.9 (197 h)                 | 9.8              | 11.9             | 52.1                               | 37.9                        | 38.3                         | 10.9                        |
| 3.2                         | 4.7              | 7.2              | 43.2                               | 26.8                        | 22.6                         | 6.7                         |
| 4.1                         | 6.6              | 8.8              | 32.8                               | 37.7                        |                              | 7.7                         |
| 3.7                         |                  |                  |                                    |                             |                              | 6.3                         |
| 1.7 (197 h)                 | 2.6              | 3.6              | 26.2                               | 27.6                        | 24.5                         | 3.2                         |
| 1.1                         | 1.7              | 2.5              | 23.5                               | 16.1                        | 20.7                         | 2.1                         |
|                             | 8.1              | 12.7             | 72.2 (216 h)                       | 101                         | 100                          | 15.9                        |
|                             | 6.0              | 8.6              | 62.9                               | 86.9                        | 127                          | 11.9                        |



TABLE II *Osteopenia idiopathica*

| Code No.                                | D-65             | D-60             | D-73             | D  |
|---|------------------|------------------|------------------|----|
| Age (years)                             | 55               | 62               | 54               | 51 |
| Sex                                     | F                | F                | F                | F  |
| Occupation                              | Factory worker   | Cashier          | Housewife        | S  |
| Weight (kg)                             | 55               | 60               | 57               | 58 |
| Radiography                             | +++++            | +++++            | +++++            | +  |
| Isotope                                 | $^{45}\text{Sr}$ | $\text{Ca}^{47}$ | $\text{Ca}^{47}$ |    |
| $k$ (liters of plasma per day)          | 2.08             | 4.51             | 5.32             |    |
| $S_1$ (liters of plasma)                | 17.5             | 31.7             | 23.0             |    |
| $S_{12}$ (liters of plasma)             | 11.8             | 20.4             | 22.0             |    |
| $k$ (liters of plasma per day)          | 7.0              | 1.3              | 2.9              |    |
| $k_1$ (liters of plasma per day)        | 3.1              | 1.5              | 0.4              |    |
| $a_i$ (% dose per 10 l plasma)          |                  |                  |                  |    |
| $t = 1$ hour                            | 56.2             | 45.1             | 40.0             |    |
| 24 hours                                | 19.6             | 18.8             | 17.5             |    |
| 120                                     | 3.8              | 7.8              | 7.0              |    |
| 240                                     | 1.4              | 4.0              | 3.1              |    |
| $\int_{t_0}^t$ (% dose per 10 l plasma) |                  |                  |                  |    |
| $t = 24$ hours                          | 30.5             | 29.6             | 24.1             |    |
| 120                                     | 84.8             | 75.2             | 67.2             |    |
| 240                                     | 76.9             | 104.8            | 91.6             |    |
| Rel (% dose)                            |                  |                  |                  |    |
| $t = 24$ hours                          | 62.8             | 91.8             | 95.4             |    |
| 120                                     | 31.8             | 77.8             | 80.8             |    |
| 240                                     | 22.8             | 70.3             | 69.5             |    |
| External counting (% of standard)       |                  |                  |                  |    |
| Knee with lowest activity               |                  |                  |                  |    |
| $t = 24$ hours                          | 36.1             | 56.8             | 21.1             |    |
| 48                                      | 29.3             |                  |                  |    |
| 168                                     | 13.8             | 47.0             | 18.2             |    |
| 236                                     | 9.9              | 40.2             | 10.9             |    |
| Thigh with lowest activity              |                  |                  |                  |    |
| $t = 24$ hours                          | 18.7             | 35.4             | 18.2             |    |
| 48                                      | 14.3             |                  |                  |    |
| 168                                     | 7.8              | 23.2             | 9.6              |    |
| 236                                     | 5.9              | 17.6             | 3.8              |    |
| L.I.V.                                  |                  |                  |                  |    |
| $t = 168$ hours                         | 30.7             | 69.6             | 57.0             |    |
| 236                                     | 15.7             | 55.8             | 53.2             |    |

TABLE II *Osteopenia idiopathica*

|       | D-99             | D-103            | E-42             | E 142            | G-13             |
|-------|------------------|------------------|------------------|------------------|------------------|
|       | 78               | 61               | 65               | 65               | 31               |
|       | F                | M                | F                | F                | F                |
|       | Housewife        | Shipyard worker  | Housewife        | Housewife        | Housewife        |
|       | 50               | 78               | 72               | 67               | 62               |
| +     | ++-++            | +++++            | +++--            | +++++            | +++-+            |
|       | Ca <sup>47</sup> | Sr <sup>90</sup> | Ca <sup>47</sup> | Sr <sup>90</sup> | Sr <sup>90</sup> |
|       | 4.20             | 3.28             | 2.73             | 3.64             | 2.50             |
|       | 20.0             | 25.0             | 23.1             | 20.7             | 19.2             |
|       | 18.7             | 24.8             | 19.5             | 19.7             | 20.9             |
|       | 2.0              | 8.9              | 0.5              | 4.7              | 8.1              |
|       | 1.6              | 2.1              | 2.3              | 1.9              | 2.8              |
|       | 50.0             | 40.0             | 43.2             | 48.3             | 52.0             |
|       | 19.7             | 18.2             | 20.5             | 18.2             | 17.0             |
|       | 7.4              | 8.2              | 10.0             | 6.0              | 3.1              |
|       | 3.4              | 2.2              | 6.0              | 2.2              | 1.0              |
|       | 32.0             | 23.0             | 26.7             | 26.0             | 29.0             |
|       | 70.6             | 86.6             | 85.4             | 66.6             | 60.3             |
|       | 103.4            | 78.0             | 124.0            | 86.0             | 69.5             |
|       | 80.9             | 81.0             | 81.7             | 82.7             | 78.7             |
|       | 70.7             | 32.9             | 76.7             | 66.6             | 33.0             |
|       | 61.7             | 39.2             | 63.0             | 48.0             | 24.1             |
|       |                  |                  | 48.1             | 24.0             |                  |
|       |                  |                  |                  | 23.1             | 24.6             |
| 92 h) | 124              | 20.4             | 24.3             | 20.7             | 10.2             |
| 34 h) | 92.1             | 12.7             | 23.5             | 13.0             | 8.2              |
|       |                  |                  | 30.6             | 16.1             |                  |
|       |                  |                  |                  | 14.2             | 7.8              |
| 92 h) | 61.7             | 7.0              | 18.4             | 8.1              | 2.7              |
| 34 h) | 43.2             | 4.4              | 12.1             | 7.2              | 3.4              |
|       | 150              | 22.7             | 75.9             | 29.5             | 19.4             |
|       | 115              | 16.6             | 69.1             | 24.2             | 13.7             |

TABLE III *Osteopenia rheumatica*

| Code No.                                      | B-33              | B-58             | C-61              | C |
|---|-------------------|------------------|-------------------|---|
| Age (years)                                   | 32                | 62               | 63                | 4 |
| Sex   | F                 | F                | F                 | F |
| Occupation                                    | Housewife         | Housewife        | Single woman      | I |
| Weight (kg)                                   | 63                | 68               | 55                | 8 |
| Radiography                                   | ++-+-             | +++--            | +++++             | - |
| Isotope                                       | Str <sup>90</sup> | Ca <sup>45</sup> | Str <sup>90</sup> |   |
| k (liters of plasma per day)                  | 4.36              | 3.39             | 4.65              |   |
| S <sub>I</sub> (liters of plasma)             | 31.3              | 19.2             | 20.8              |   |
| S <sub>II</sub> (liters of plasma)            | 31.7              | 22.0             | 16.0              |   |
| k <sub>0</sub> (liters of plasma per day)     | 9.1               | 3.1              | 8.3               |   |
| k <sub>I</sub> (liters of plasma per day)     | 2.3               | 1.5              | 2.2               |   |
| a <sub>I</sub> (% dose per 10 l plasma)       |                   |                  |                   |   |
| t = 1 hour                                    | 32.0              | 52.0             | 48.0              |   |
| 24 hours                                      | 12.5              | 20.0             | 16.0              |   |
| 120   | 3.7               | 9.0              | 4.3               |   |
| 240   | 1.3               | 4.5              | 1.7               |   |
| $\int_0^t a_I$ (% dose per 10 l plasma)       |                   |                  |                   |   |
| t = 24 hours                                  | 19.0              | 23.0             | 24.0              |   |
| 120   | 47.0              | 78.0             | 59.5              |   |
| 240   | 58.3              | 110.0            | 73.7              |   |
| Ret (% dose)                                  |                   |                  |                   |   |
| t = 24 hours                                  | 74.5              | 90.8             | 77.5              |   |
| 120   | 46.3              | 71.8             | 54.7              |   |
| 240   | 34.0              | 60.0             | 46.7              |   |
| External counting<br>( $\sigma$ = 1 standard) |                   |                  |                   |   |
| Knee with lowest activity                     |                   |                  |                   |   |
| t = 24 hours                                  | 25.3              | 62.0             | 22.0              |   |
| 48  | 26.5              |                  | 20.4              |   |
| 168   | 17.3              | 75.3             | 11.6              |   |
| 206   | 13.1              | 37.1             | 8.0               |   |
| Thigh with lowest activity                    |                   |                  |                   |   |
| t = 24 hours                                  | 11.9              | 29.5             | 10.3              |   |
| 48  | 9.0               |                  | 8.6               |   |
| 168   | 6.1               | 19.7             | 6.7               |   |
| 206   | 3.6               | 8.2              | 5.7               |   |
| L IV  |                   |                  |                   |   |
| t = 168 hours                                 |                   |                  | 12.8              |   |
| 206   |                   |                  | 12.9              |   |

TABLE III. *Osteopenia rheumatica*

| C-134             | D-67             | D-74             | E 9              | E-93             |
|-------------------|------------------|------------------|------------------|------------------|
| 39                | 52               | 48               | 57               | 72               |
| F                 | F                | F                | M                | M                |
| Office-<br>worker | Housewif         | Housewif         | Painter          | Carpenter        |
| 51                | 50               | 51               | 78               | 62               |
| ++-++             | ++-++            | ++-++            | ++-++            | ++-++            |
| Sr <sup>88</sup>  | Sr <sup>88</sup> | Sr <sup>88</sup> | Ca <sup>47</sup> | Ca <sup>47</sup> |
| 6.43              | 3.01             | 4.43             | 1.25             | 2.82             |
| 20.7              | 18.4             | 20.1             | 30.0             | 23.1             |
| 23.4              | 17.4             | 20.7             | 9.6              | 18.8             |
| 9.7               | 4.8              | 2.7              | 1.4              | 2.4              |
| 2.8               | 5.0              | 2.0              | 2.9              | 1.1              |
| 43.0              | 34.4             | 49.7             | 33.4             | 39.8             |
| 13.0              | 19.6             | 18.5             | 21.5             | 19.0             |
| 2.1               | 3.8              | 6.3              | 10.5             | 9.0              |
| 0.5               | 0.9              | 2.7              | 6.3              | 5.0              |
| 23.0              | 32.0             | 28.4             | 28.5             | 28.0             |
| 44.8              | 67.3             | 69.7             | 85.8             | 79.2             |
| 50.5              | 70.9             | 91.4             | 137.8            | 113.4            |
| 72.1              | 79.9             | 88.0             | 88.5             | 91.5             |
| 44.1              | 40.4             | 68.0             | 63.6             | 73.6             |
| 36.3              | 28.3             | 86.7             | 48.9             | 60.8             |
| 21.4              | 28.9             | 28.8             | 41.6             |                  |
| 17.1              |                  | 27.3             |                  | 75.5             |
| 7.2               | 9.0              | 16.6             | 28.2             | 68.0             |
| 5.4 (312 h)       | 4.8 (300 h)      | 11.2             | 21.0             | 37.4             |
| 6.1               | 13.1             | 9.4              | 26.2             |                  |
| 4.6               |                  | 7.8              |                  | 51.8             |
| 1.8               | 5.0              | 4.1              | 15.6             | 39.9             |
| 1.4 (312 h)       | 3.1 (360 h)      | 2.8              | 12.8             | 24.8             |
| 9.1               | 14.1             | 29.7             | 42.9             | 173              |
| 6.9 (312 h)       | 9.3 (360 h)      | 32.2             | 30.8             | 121              |

TABLE V Osteopenia, treated

| No.<br>years)                        | D-31<br>66<br>F          | D-40<br>60<br>F          | D-43<br>60<br>F          | D-61<br>49<br>M          |
|--------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Profession                           | Housewife                | Child<br>servant         | Housewife                | Salesman                 |
| Height (kg)                          | 81                       | 66                       | 65                       | 81                       |
| Graph                                | +++++                    | +--+                     | +--+                     | +--+                     |
| Medic agent                          | Duraboline®              | Duraboline®              | Duraboline®              | Duraboline®              |
| Duration of treatment (months)       | 18                       | 7                        | 22                       | 6                        |
| Diagnosis                            | Osteopenia<br>Idiopathic | Osteopenia<br>Idiopathic | Osteopenia<br>Idiopathic | Osteopenia<br>Idiopathic |
| Pre-treatment                        | Se <sup>25</sup>         | Se <sup>25</sup>         | Se <sup>25</sup>         | Ca <sup>25</sup>         |
| (liters of plasma per day)           | 3.82                     | 3.47                     | 2.49                     | 1.88                     |
| (liters of plasma)                   | 24.4                     | 18.6                     | 31.8                     | 26.3                     |
| (liters of plasma)                   | 19.2                     | 21.0                     | 26.4                     | 20.6                     |
| (liters of plasma per day)           | 2.9                      | 5.3                      | 6.8                      | 2.3                      |
| (liters of plasma per day)           | 1.3                      | 2.6                      | 3.4                      | 2.0                      |
| Post-treatment dose per 10 l plasma: |                          |                          |                          |                          |
| 24 hours                             | 43.0                     | 53.8                     | 31.4                     | 38.0                     |
| 120 hours                            | 19.0                     | 17.2                     | 12.7                     | 18.2                     |
| 120                                  | 6.6                      | 4.6                      | 4.9                      | 8.6                      |
| 240                                  | 3.4                      | 1                        | 2.4                      | 5.4                      |
| Post-treatment dose per 10 l plasma: |                          |                          |                          |                          |
| 24 hours                             | 26.0                     | 27.0                     | 18.0                     | 24.7                     |
| 120                                  | 71.8                     | 63.1                     | 49.7                     | 73.0                     |
| 240                                  | 96.0                     | 78.2                     | 67.4                     | 108.1                    |
| Post-treatment dose:                 |                          |                          |                          |                          |
| 24 hours                             | 62.8                     | 62.8                     | 78.4                     | 68.8                     |
| 120                                  | 71.6                     | 49.7                     | 43.9                     | 67.8                     |
| 40                                   | 39.4                     | 27.0                     | 33.3                     | 54.6                     |
| Final counting                       |                          |                          |                          |                          |
| Standard                             |                          |                          |                          |                          |
| Lowest activity                      |                          |                          |                          |                          |
| 24 hours                             | 37.3                     | 31.4                     |                          | 70.7                     |
| 48                                   | 26.7                     | 28.6                     |                          | 60.2                     |
| 168                                  | 19.3                     | 17.8                     | 15.2                     | 49.9                     |
| 336                                  | 1.9                      | 16.2                     | 10.8                     | 45.6 (258 h)             |
| High with lowest activity            |                          |                          |                          |                          |
| 24 hours                             | 8.4                      | 11.3                     |                          | 48.0                     |
| 48                                   | 7.8                      | 9.2                      |                          | 41.3                     |
| 168                                  | 4.8                      | 5.2                      | 4.8                      | 30.1                     |
| 336                                  | 3.5                      | 3.4                      | 3.2                      | 25.8 (258 h)             |
| Final                                |                          |                          |                          |                          |
| 168 hours                            | 22.0                     | 23.8                     | 30.3                     |                          |

TABLE V *Osteopenia treated*

| D-73                      | D-95                      | Additional case                           |                     |
|---------------------------|---------------------------|---|---------------------|
|                           |                           | D-30                                      | D-30                |
| 55                        | 52                        | 36  | 37                  |
| F                         | F                         | F   | F                   |
| Housewife                 | Seamstress                | Saleslady                                 |                     |
| 81                        | 81                        | 42  | 42                  |
| +++++                     | +++++                     | + - + - -                                 | + - + - -           |
| Duraboline®               | Duraboline®               |   | Deca<br>Duraboline® |
| 6                         | 6                         |   | 11                  |
| Osteopenia<br>Idiopathica | Osteopenia<br>Idiopathica | Lupus erythem. dis.<br>On corticosteroids |                     |
| Ca <sup>47</sup>          | Ca <sup>47</sup>          | Sr <sup>86</sup>                          | Sr <sup>86</sup>    |
| 3.46                      | 3.06                      | 2.16                                      | 2.09                |
| 22.5                      | 18.7                      | 18.8                                      | 16.9                |
| 22.4                      | 14.6                      | 16.0                                      | 14.7                |
| 1.3                       | 1.9                       | 4.5                                       | 5.7                 |
| 0.6                       | 2.0                       | 2.0                                       | 2.1                 |
| 41.4                      | 52.6                      | 63.2                                      | 59.3                |
| 19.5                      | 24.7                      | 24.9                                      | 21.3                |
| 8.9                       | 11.8                      | 6.0                                       | 5.1                 |
| 6.1                       | 8.0                       | 1.6                                       | 1.7                 |
| 26.0                      | 36.5                      | 39.9                                      | 35.0                |
| 77.8                      | 106.0                     | 88.3                                      | 77.2                |
| 112.9                     | 149.6                     | 103.2                                     | 93.2                |
| 96.3                      | 93.4                      | 81.5                                      | 74.2                |
| 87.0                      | 79.9                      | 47.6                                      | 40.8                |
| 80.2                      | 70.4                      | 30.3                                      | 27.8                |
| 29.6                      | 56.1                      | 21.0                                      | 29.3                |
| 30.3                      | 40.2                      | 18.2                                      |                     |
| 21.1                      | 34.7                      | 8.4                                       | 10.0                |
|                           |                           | 4.8                                       | 5.7                 |
| 27.1                      | 38.5                      | 5.9                                       | 8.0                 |
| 19.6                      | 23.9                      | 4.5                                       |                     |
| 12.9                      | 21.4                      | 2.2                                       | 2.2                 |
|                           |                           | 1.2                                       | 1.8                 |
| 78.7                      | 69.2                      | 17.2                                      |                     |
| 61.7                      | 61.7                      | 11.9                                      |                     |

TABLE VI Parathyroid disease

| Code No.  | E 120               | E 120            | F-88             | F-80                        |    |
|---|---------------------|------------------|------------------|-----------------------------|----|
| Age (years)   | 42                  | 43               | 49               | 79                          |    |
| Sex   | F                   | F                | F                | M                           |    |
| Occupation  | Housewife           |                  | Housewife        | Factory foreman             |    |
| Weight (kg)   | 50                  | 51               | 61               | 80                          |    |
| Radiography   | Extensive changes   | Small changes    | Osteomegaly?     | -----                       |    |
| Diagnosis   | Sec hyper parathyrt | Treated 6 months | Hypoparathyrt    | Prim. parathyrt hyperplasia |    |
| Ca/ (mEq per litre)   | 5.0                 | 5.1              | 2.8              | 5.8                         |    |
| P/ (mg per 100 ml)  | 6.6                 | 6.8              | 6.2              | 2.1                         |    |
| Alk. phosph. (units)  | 22                  | 7                | 3                | 8                           |    |
| Isotope   | Ca <sup>47</sup>    | Ca <sup>47</sup> | Sr <sup>86</sup> | Sr <sup>86</sup>            |    |
| k (liters of plasma per day)  | 14.15               | 8.51             | 0.75             | 9.14                        |    |
| S <sub>I</sub> (liters of plasma)                                   | 37.9                | 21.2             | 19.7             | 21.4                        |    |
| S <sub>II</sub> (liters of plasma)                                  | 46.0                | 28.7             | 16.6             | 26.5                        |    |
| k <sub>0</sub> (liters of plasma per day)                           | 0.4                 | 0.5              | 2.3              | 9.7                         |    |
| k <sub>f</sub> (liters of plasma per day)                           | 1.5                 | 0.7              | 1.6              | 1.2                         |    |
| a <sub>1</sub> (% dose per 10 l plasma)                             |                     |                  |                  |                             |    |
| t = 1 hour  | 23.9                | 47.2             | 50.8             | 21.8                        | 41 |
| 24 hours  | 9.5                 | 15.9             | 33.0             | 11.0                        | 15 |
| 120   | 2.7                 | 4.3              | 9.3              | 2.2                         | 2  |
| 240   | 1.5                 | 2.9              | 4.3              | 0.7                         | 2  |
| ∫ <sub>0</sub> <sup>t</sup> a <sub>1</sub> (% dose per 10 l plasma) |                     |                  |                  |                             |    |
| t = 24 hours  | 18.5                | 25.8             | 33.0             | 19.0                        | 18 |
| 120   | 36.8                | 27.0             | 90.6             | 30.7                        | 49 |
| 240   | 46.9                | 72.6             | 124.8            | 46.2                        | 58 |
| Ret (5 dose)  |                     |                  |                  |                             |    |
| t = 24 hours  | 95.7                | 96.5             | 88.0             | 53.2                        | 90 |
| 120   | 92.4                | 92.3             | 60.2             | 59.1                        | 79 |
| 240   | 91.0                | 90.4             | 36.3             | 49.6                        | 75 |
| External counting<br>(% of standard)                                |                     |                  |                  |                             |    |
| Knee with lowest activity   |                     |                  |                  |                             |    |
| t = 94 hours  | 103                 | 97.6             |                  |                             |    |
| 48  | 90.3                |                  |                  | 18.3 (72 h)                 | 36 |
| 168   | 113                 | 92.6             | 34.5             | 12.2                        | 25 |
| 336   | 96.0                | 67.0             | 25.8             | 9.5                         | 26 |
| Thigh with lowest activity  |                     |                  |                  |                             |    |
| t = 24 hours  | 59.2                | 43.7             |                  |                             |    |
| 48  | 49.5                |                  |                  | 6.9 (72 h)                  | 19 |
| 168   | 52.6                | 32.1             | 15.7             | 4.2                         | 18 |
| 336   | 56.7                | 18.0             | 10.8             | 3.0                         | 14 |

| G-14                | G 116                 | G-126                   | A-4                   | A-4               | A-4                 |
|---------------------|-----------------------|-------------------------|-----------------------|-------------------|---------------------|
| 51                  | 25                    | 58                      | 55                    | 55                | 56                  |
| M                   | F                     | F                       | M                     | M                 | M                   |
|                     | Office-<br>worker     | Housewife               | Hospital<br>orderly   |                   |                     |
| 76                  | 53                    | 73                      | 60                    | 58                | 63                  |
| Osteitis<br>fibrosa | -----                 | -----                   | +-----                | +-----            | +-----              |
| 4 months<br>postop  | Chief-cell<br>adenoma | Hypopara-<br>thyroidism | Nephro-<br>calcinosis | 7 days<br>post p. | 11 months<br>postop |
| 5.0                 | 7.1                   | 2.9                     | 4.7                   | 4.6               | 4.6                 |
| 2.0                 | 1.8                   | 5.5                     | 2.6                   | 2.7               | 2.6                 |
| 9                   | 11                    | 4                       | 7                     | 6                 | 6                   |
| Ca <sup>47</sup>    | Ca <sup>47</sup>      | Ca <sup>47</sup>        | Sr <sup>90</sup>      | Sr <sup>90</sup>  | Ca <sup>47</sup>    |
| 9.16                | 8.06                  | 13.7                    | 11.07                 | 4.45              | 5.14                |
| 27.4                | 19.5                  | 31.1                    | 27.9                  | 23.8              | 20.9                |
| 33.7                | 26.6                  | 17.9                    | 50.8                  | 21.8              | 28.2                |
| 0.3                 | 3.2                   | 0.5                     | 4.7                   | 5.0               | 1.1                 |
| 9.8                 | 0.6                   | 2.5                     | 3.1                   | 2.8               | 1.7                 |
| 36.5                | 53.9                  | 47.5                    | 35.9                  | 42.1              | 47.8                |
| 12.2                | 14.0                  | 21.5                    | 9.0                   | 15.3              | 16.7                |
| 8.4                 | 2.5                   | 9.8                     | 3.4                   | 4.3               | 7.6                 |
| 3.0                 | 1.5                   | 7.0                     | 1.1                   | 1.8               | 3.7                 |
| 19.0                | 23.5                  | 28.5                    | 15.0                  | 23.6              | 24.2                |
| 50.2                | 52.3                  | 85.4                    | 39.2                  | 57.3              | 60.6                |
| 70.4                | 64.1                  | 126.4                   | 48.5                  | 71.5              | 96.3                |
| 93.9                | 83.1                  | 88.3                    | 87.4                  | 79.5              | 94.3                |
| 94.9                | 69.8                  | 73.9                    | 69.5                  | 86.6              | 84.7                |
| 91.7                | 63.2                  | 63.1                    | 62.5                  | 44.5              | 73.1                |
| 90.4                | 51.8                  | 47.8                    |                       | 33.2              |                     |
|                     | 46.6                  |                         | 26.2                  |                   | 83.6                |
| 89.2                | 37.2                  | 41.6                    | 14.2                  | 18.6              | 70.2                |
| 76.2                | 33.7                  | 38.7                    | 6.6                   | 17.0              | 52.9                |
| 84.6                | 36.9                  | 27.8                    |                       | 12.5              |                     |
|                     | 37.5                  |                         | 7.3                   |                   | 46.1                |
| 83.7                | 19.4                  | 22.4                    | 4.3                   | 7.3               | 30.9                |
| 44.2                | 19.4                  | 19.6                    | 3.0                   | 6.2               | 22.5                |
| 113                 | 64.1                  | 66.3                    | 22.4                  | 39.2              |                     |
| 105                 | 54.3                  | 44.9                    | 18.4                  | 31.8              |                     |





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**The Distribution of  
Erythrocytes and Reticulocytes in  
Blood Smears**



FROM THE MEDICAL DEPARTMENT B, UNIVERSITY OF BERGEN  
SCHOOL OF MEDICINE. (HEAD PROFESSOR JOHS. BOE)

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The Distribution of  
Erythrocytes and Reticulocytes in  
Blood Smears

By  
PER STAVEM

Printed in Norway by  
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## Preface

This work was carried out in the years 1960—1963 while I was serving as assistant physician at the Medical Department B University of Bergen, School of Medicine.

I wish to express my thanks to Professor John. Bøe, head of the department, for his continuous encouragement and interest in my work.

Dr. Tachidi Madsen was kind enough to read the manuscript. I gratefully acknowledge the many helpful suggestions he made by way of improving the text.

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Bergen May 1963

*Perr Stålen.*



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## Introduction

As part of some experimental work on mice in 1960—1961 I performed a large number of reticulocyte counts. My observed differences between duplicate counts were considerably larger than some of the differences reported in the literature.

This discrepancy between the chance fluctuations of my counts and some of those reported in the literature, prompted me to do some investigations of observed and theoretical counting errors.

Among the many workers who have reported values for erythrocyte chamber counts in their publications, only a few have calculated their observed standard deviation of individual counts. This standard deviation of individual counts is an expression of the degree of uniformity of distribution of the erythrocytes. When it comes to the observed distribution of erythrocytes in a blood smear I have been unable to find any publications.

A few authors have been interested in the theoretical distribution of erythrocytes in a counting chamber or a blood smear. Some of them have found it likely that the erythrocytes will be randomly distributed, the number of individuals in areas similar in size thus following the Poisson distribution.

It has sometimes been maintained that the size of the erythrocytes will cause a crowding effect resulting in a distribution slightly more uniform than a Poisson distribution. Models allowing for this crowding effect have been published. These models compare the erythrocytes to equal

discs randomly distributed in a fixed number of available spaces. From these models the expected standard deviations for randomly distributed discs, may be calculated.

I was not quite convinced that these models gave a really good description of a random distribution of discs, and decided to do some experimental work in this field. My first task was an attempt to find a mathematical expression for the distribution of one set of randomly placed discs. The next task was an attempt to find out if erythrocytes in a blood smear followed this distribution.

The reticulocytes are often believed to be randomly mixed among the other erythrocytes. The error of a reticulocyte count will then be given by the standard deviation for a binomial or Bernoulli distribution.

Some authors, however, frankly state that they can not a priori accept that the reticulocytes follow the binomial distribution and that their observations are that the reticulocytes are much more uniformly distributed.

Because of these discrepancies, I decided to do some experimental work in this field using two sets of equalized discs, which were randomly placed as well as randomly mixed. My first task was an attempt to find a mathematical expression for the distribution of each of the two sets of discs. The next task was an attempt to find out if reticulocytes in a blood smear follow this distribution.



# Survey of literature and outline of the present problem

## A. Distribution of erythrocytes

### 1 Distribution of erythrocytes in counting chambers

#### a) *Theoretical distribution error*

The distribution of erythrocytes in a smear has received very little if any interest in previous literature. The distribution of erythrocytes in a counting chamber however has been the subject of numerous publications. We think a survey of these publications will be of interest, as the distribution in a smear might prove to differ little from that in a counting chamber. Some of the theoretical models applied to the chamber situation, might be found to fit the smear situation just as well, or possibly even better.

We shall merely touch a few developments of statistical control in bacteriology as an introduction to the somewhat similar problem in hematology. In bacteriology the type of distribution of bacteria and yeast cells in a well mixed suspension has for some time been generally accepted (29-34). Various methods of statistical control in that field have been developed largely due to Fisher and co-workers (29).

The French mathematician Poisson discovered the distribution which is named after him as the Poisson distribution describing the frequency of occurrence of rare events. If the probability of an event

is exceedingly small, but remains constant, the number of occurrences will be distributed as the Poisson series. Suicides of children per year in Prussia has been used as an example of a Poisson distribution (13). If the mean number of suicides is  $m$ , the frequency of years with 0 1 2 individuals will be given in terms of the exponential

$$\lambda^x = (1 + m + \frac{m^2}{2!} + \frac{m^3}{3!} + \dots)$$

where  $\lambda$  is the number of years and  $m$  the mean number of suicides per year and  $e$  is the base of the natural or Napierian system of logarithms.

The mean squared deviations from the mean ( $m$ ) gives the observed variance of individual number per division. For a Poisson distribution the expected variance is equal to the mean ( $m$ ). When  $m$  has a large value the distribution of numbers approximates closely to the normal form, and  $\sqrt{m}$  can be taken to represent the standard deviation of individual number per division.

Student\* (83) conceived the hypothesis that when yeast cells in a well mixed suspension were counted in a hemacytometer the cells would be randomly placed, and therefore the number counted in each

The famous pseudonym of the great statistician W. S. Gosset.

division would follow the Poisson distribution. From the mean number per division "Student" could calculate the expected frequency of divisions with 0 1 2

cells. These expected frequencies agreed very well with the observed frequencies. It has gradually become widely appreciated that yeast cells and bacteria in a well mixed suspension are randomly distributed.

If we are counting yeast cells in a hemacytometer the observed and expected frequencies can be compared by means of the Goodness of Fit method. If our technique is poor the observed and expected frequencies may differ considerably. Similarly if the same volume of a well mixed bacterial suspension is placed on each of a number of plates, the frequency of plates growing 0, 1, 2 bacterial colonies will follow the Poisson distribution.

This knowledge of the random distribution of yeast cells and bacteria in a well mixed suspension, is the very basis for the now widely appreciated statistical control in bacteriology. If an observed distribution is much more uniform than expected for a Poisson distribution, there is something wrong. And, on the opposite hand, if the distribution is much more irregular than expected, the technique for diluting, mixing, counting or something else is probably defective.

In 1878 Abbe (1) concerned the hypothesis that the erythrocytes in a well mixed dilution were randomly distributed. By probability calculations he found the expected standard deviation (S.D.) for an individual erythrocyte count to be  $\sqrt{m}$  where  $m$  was the number of erythrocytes counted. He did not himself attempt to test his hypothesis against observations.

Three years later Lyon & Thomas (60) however found the observed S.D. of individual erythrocyte counts to come very

close to the expected value calculated by Abbe's formula.

In 1907 when "Student" (83) published his fundamental work on distribution of yeast cells in the hemacytometer he was unaware of Abbe's and Lyon & Thomas' previous work. As a matter of fact he was also unaware of Poisson's previous work, and independently developed the Poisson distribution of rare event himself. "Student" (84) also mentioned deviations from the Poisson distribution in cases where the presence of one individual influences the chance of others falling into that division. In the case of clumping of bacteria the chances would be increased. In case of large cells in a hemacytometer count the chances would be decreased, the distribution therefore being slightly more uniform than a Poisson distribution.

Berkson, Magath and Hurn (5) in 1935 published some very careful hemacytometer counts by a photographic method. All the counts were effected by photographing the hemacytometer field and subsequently pricking through each cell on the photograph with a stylus connected to an electric counter. The photographs were afterwards scrutinized against the light to check that each cell was pierced once and only once. The method was thought to allow of no error in the technique of enumeration. Berkson et al counted erythrocytes in 400 divisions sized 1/400 mm in each of 10 samples of normal blood diluted 1:200. The number of erythrocytes counted with their very careful photographic technique, was around 2,500 for each of the 10 samples.

The observed variance of individual number per division was  $0.85 \times m$  whereas a variance of  $m$  would have been expected for a Poisson distribution with a mean of  $m$ . Berkson et al thought this deviation from the Poisson distribution

was due probably to a crowding effect of the cells in the chamber" Berkson et al. did not attempt to arrive at a theoretical model for this crowding effect. Berkson (4) expected the same fraction (0.85) of  $m$  for variance when the blood count was 4 millions as when it was 6 millions erythrocytes per mm. blood. This might seem somewhat surprising as one might think the crowding effect would be more marked with a higher blood count.

Engbott (30) in 1937 studied the crowding mechanism. He suggested that one could consider the erythrocytes on the bottom of the counting chamber as occupying randomly some of a limited number of available spaces, and that the situation therefore would agree best with a binomial distribution. From the well known formula for the variance of a binomial distribution, Engbott arrived at a formula for the variance of individual number of erythrocytes per division. For a binomial distribution the variance is  $pqn$  where for Engbott's model  $p$  is the chance that a space is occupied by an erythrocyte,  $q$  the chance that it is not occupied and  $n$  the number of available spaces per division. If  $m$  is the mean number of erythrocytes per division, and  $n$  the number of available spaces per division, the chance  $p$  of a space being occupied by an erythrocyte, is  $\frac{m}{n}$ . The chance  $q$  of a space not

being occupied, is  $(1 - \frac{m}{n})$ . The formula for the variance of individual number of erythrocytes per division will thus be variance =  $\frac{m}{n} (1 - \frac{m}{n}) n$ , or  $m - \frac{m^2}{n}$ . For divisions are 1400 mm. and usual erythrocyte size Engbott calculated the number of available spaces, that is the maximal number of erythrocytes, to be slightly more than 40. He used 40 when calculating

expected variance for counts with  $m$  varying from 5.55 to 7.83 and found good fits with observed counts.

Engbott's model will be just like having a number  $n$  of holes in each division, a random number of these holes being occupied by erythrocytes, to give a mean number of  $m$  erythrocytes per division. If all chamber divisions are filled to a maximum, all holes are occupied, and all divisions contain exactly  $n$  erythrocytes. The variance of individual number per division will then be zero as can also be seen from the formula variance

$$= m - \frac{m^2}{n} \quad \text{which will be zero when } m = n.$$

In 1937 Turner & Eadie (23) and Hamaker (43) apparently without knowing Engbott's work 20 years earlier suggested the same binomial model. They calculated the number ( $n$ ) of available spaces per division by assuming a uniform quadratic arrangement of the erythrocytes (fig. 1). Because of the dead space between the erythrocytes, each cell will occupy about 1.273 times its mean plane area.

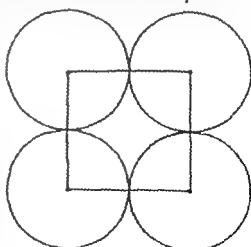


Fig. 1 Discs in uniform quadratic arrangement.

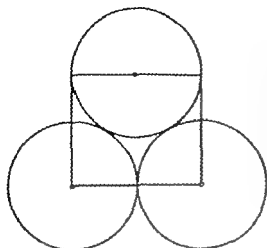


Fig. 2. Discs in the most compact, triangular arrangement.

Watanabe (86-87) apparently without knowing Enghoff's and Turner & Eadie's previous works, also used the same binomial model considering the erythrocytes as occupying randomly some of a limited number of available spaces. A slight difference is the fact that Watanabe calculated the number of available spaces by assuming a uniformly triangular arrangement of the erythrocytes (fig. 2). This is the case of the most compact cellular arrangement. The dead space between the erythrocytes is smaller than for the quadratic arrangement and each cell will occupy about 1.02 times its mean plane area. Watanabe assumed the diameter of erythrocytes in the counting chamber to be on the average  $7.7 \mu$  and the maximal number per 1.400 mm<sup>2</sup> division may thus be calculated to 48.685. If Turner & Eadie's quadratic arrangement was assumed, the same diameter of  $7.7 \mu$  would give us a maximal number of 42.2 per division.

In 1950 Lancaster (52) attacked the problem of the crowding effect. He counted erythrocytes in 400 divisions sized 1.400

mm in each of 52 samples of diluted blood. He adjusted the dilutions to make the mean number of erythrocytes per division range from as low as 1/20th of the number for a normal count, and up to as high as corresponding to a count in blood containing 6.4 mill. erythrocytes per mm diluted the usual 1:200. From his 52 counts Lancaster calculated an empirical formula for the variance of individual number of cells per division, a formula which allowed for the crowding effect.

His formula was  $\text{variance} = m - \frac{m^2}{48.6}$

where  $m$  was mean number per division.

Using Berkson *et al.*'s counts (5) Lancaster calculated another empirical formula for the variance

$\text{variance} = m - \frac{m^2}{38}$ , which gave the best fit for Berkson *et al.*'s counts.

We may now compare the formulae for variance according to Enghoff, Turner & Eadie, Watanabe, and Lancaster

Enghoff  $\text{variance} = m - \frac{m^2}{40}$

Turner & Eadie  $\text{variance} = m - \frac{m^2}{42.2}$   
(For erythrocyte diameter of  $7.7 \mu$ .)

Watanabe  $\text{variance} = m - \frac{m^2}{48.7}$

Lancaster from own counts  $\text{variance} = m - \frac{m^2}{48.6}$

Lancaster from Berkson *et al.*'s counts  $\text{variance} = m - \frac{m^2}{38}$

As we can see, the 4 formulae are very similar. And their originators have all found good fits with observed counts. The formulae have been tested for densities of cells as high as or lower than the densities normally encountered during chamber counts. For that matter we might use one

of these 4 formulae if we wanted a formula which took into account the slight crowding effect in normal chamber counts.

It would, however be of considerable theoretical interest to test if these 4 formulae also will give a good fit at maximal or close to maximal densities of erythrocytes. This might not necessarily be the case, as it is a well known fact in biology that theoretical models or formulae can give satisfactory approximations within a certain area, but prove quite useless when tested at extreme values of a variable.

#### b) *Observed total error of erythrocyte counts*

During the last 100 years numerous authors have published accounts of their observed standard deviation (S. D.) of individual erythrocyte counts, only rarely compared to expected values for a hypothetical model. Most of the authors have calculated the S. D. from a number of duplicate counts from the same sample or patient, or from a large number of counts of the same sample. In the first case they have usually employed the formula

$$S. D. = \pm \sqrt{\frac{\sum (Difference^2)}{2n}} \quad \text{where}$$

difference is the difference between the two counts of each duplicate and  $n$  is the number of duplicate counts, the number of pairs to speak. In the second case they have employed the formula

$$S. D. = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}} \quad \text{where } x \text{ is the}$$

mean count  $x$  is the individual counts observed and  $n$  is the total number of counts.

These calculations would give the total S. D. of an individual erythrocyte count.

#### c) *Observed pipette error*

If the multiple or duplicate counts are done with different pipettes, a slight difference in volume capacity between the pipettes will contribute to the observed total error of the erythrocyte count. Such a difference between pipettes which are manufactured to hold the same volume, has been investigated by several authors (5 6 10 19 55 61)

When the pipettings are done by only one person, using constant, careful technique with the same pipette all the time, the pipette and the pipetting error can be almost disregarded (18, 71)

#### d) *Observed chamber error*

Just as with the pipettes, the counting chambers do not necessarily hold exactly the volume they are manufactured to hold. Contribution to total error due to differences between chambers has also been investigated by several authors (5 6 10 19 55 61) and as with pipettes, when the same person uses the same chamber all the time, the chamber error will be almost eliminated.

#### e) *Observed distribution error*

If one endeavors to compare the distribution errors reported in the literature by various authors, one must hope that the chambers did not have any systematized defects, like being deeper on one side than the other. One must also hope that the technique of filling was adequate and fairly similar.

The basis for assessing the distribution error is the variability in number of erythrocytes in different counts or in different divisions of the chamber. If there is no systematized difference in the density of erythrocytes between different parts of the



chamber it will not matter which divisions from the entire grid are used. If there, however, does exist a systematized difference within the grid as some authors have found (19 48 55 63 75) the observed distribution error will to a certain degree depend on which divisions are used for the count. The reported systematized difference consists of a decreased density of cells on the side of filling and an increased density on the opposite side. The greater the speed of loading the more pronounced is this systematized difference (63). A possible explanation should be that the cells during the process of filling receive a momentum which tends to carry more of the cells to the side opposite to that of filling.

This systematized difference in density of cells being a definite possibility a comparison of observed distribution errors from the literature will have to take into account which parts of the grid are counted.

1 Some authors have counted in all 400 small divisions (each  $1/400$  mm<sup>2</sup>) in the central 1 mm of the grid calculating the observed variance of individual number per divisions (5 6 52, 61). Enghoff (30) counted in 100 small divisions ( $1/400$  mm<sup>2</sup>) which probably were scattered over a larger area than 1 mm<sup>2</sup> as his counting chamber evidently had an unmodified Burkner ruling.

2 Some authors have calculated an index of dispersion from a series of counts in 5 divisions (26 52). One hundred such indices should follow a known pattern if the erythrocytes are following the Poisson distribution (34 35).

3 Another method has been first to make one count in a certain number of divisions of the grid, and then to continue counting in another equally many divisions on the same grid (37).

4 Other authors have used the same chamber and coverglass, and have made a number of different counts from the same 1:200 blood dilution which has been thoroughly shaken each time (18 21 32, 38, 44 71). Lyon & Thoma (60) made a number of counts on the same undiluted samples and blood. They used the same pipettes for dilution each time, however and the pipetting error was probably very small.

A possible systematized difference in density of cells between the side of filling and the opposite side, would hardly influence the observed distribution error as assessed by method 1 provided all divisions are located within the same 1 mm<sup>2</sup> area. The same applies to method 2, provided that each of the 100 indices is based on counts in 5 neighboring divisions. When method 3 is used, on the other hand a systematized difference might cause the observed distribution errors to appear somewhat higher. If exactly the same divisions are counted each time, a systematized difference in density might not affect the observed distribution error when method 4 is used. With method 4 however a possible slight difference in the manner of filling the chamber including the positioning of the coverglass, might cause an increase in the observed distribution error.

In table 1 are listed some observed distribution errors from the literature. Except for the observations of Lyon & Thoma (60) all the listed counts were made on human blood. Lyon & Thoma used pig's blood. (Pig's blood has a mean erythrocyte count of 7.93 millions per mm<sup>3</sup> mean diameter of  $5.5 \mu$  and hematocrit of 46.3 (91)). The blood dilution was for all the listed counts 1:200. In the last column of table 1 the observed standard deviation of individual number of erythrocytes is given as a fraction of  $\sqrt{n}$ .

Table 1 Observed S. D. of individual erythrocyte count, given as fraction of the S. D. expected for a Poisson distribution with the same mean. (From the literature).

| Author                        | No. of counts | Average red cells before dilution (millions) | Area counted (mm <sup>2</sup> ) | Average no. of red cells per count (m) | S. D. exp. for Poisson distrib. ( $\sqrt{m}$ ) | Obs. S. D. as fraction of $\sqrt{m}$ |
|-------------------------------|---------------|--|---------------------------------|--|--|--------------------------------------|
| Lyon & Thomas (60)            | 24+12<br>+12  | 8.38   | 0.25                            | 1047.5                                 | 32.4   | 0.3                                  |
| Burker (18)                   | 7             | 5.28   | 0.2                             | 328                                    | 23   | 2                                    |
| Burker (19)                   | 7             | 5.37   | 0.4                             | 1074                                   | 32.8   | 1.5                                  |
| Burker (18)                   | 7             | 5.35   | 0.8                             | 2140                                   | 46.3   | 1.5                                  |
| Czerniadyk (21)               | 14            | 5.105  | 0.4                             | 1021                                   | 32.0   | 1.5                                  |
| Hansen (44)                   | 10 x 2        | 4.72   | 0.                              | 1179                                   | 34.3   | 1.5                                  |
| Fenchel (32)                  | 30            | 4.91   | 0.4225                          | 1039.46                                | 32.2   | 1.5                                  |
| Glatzel (38)                  | 6             | 4.66   | 0.2                             | 466                                    | 21.6   | 1.5                                  |
| Berkson & al. (5)             | 400 x 10      | 4.8  | 0.0025                          | 6.005                                  | 2.45   | 1.5                                  |
| Plum (71)                     | 4 x 1         | 4.61   | 0.2                             | 461                                    | 21.5   | 1.5                                  |
| Plum (71)                     | 20 x 17       | 4.61   | 0.04                            | 92.2                                   | 9.6  | 1.5                                  |
| Engelhoff (30)                | 100 x 28      | 4.3  | 0.0025                          | 5.35                                   | 2.31   | 1.5                                  |
| Engelhoff (30)                | 100 x 126     | 4.7  | 0.0025                          | 3.86                                   | 2.42   | 1.5                                  |
| Engelhoff (30)                | 100 x 173     | 5.1  | 0.0025                          | 6.35                                   | 2.52   | 1.5                                  |
| Engelhoff (30)                | 100 x 85      | 5.5  | 0.0025                          | 6.87                                   | 2.62   | 1.5                                  |
| Engelhoff (30)                | 100 x 19      | 6.5  | 0.0025                          | 7.83                                   | 2.8  | 1.5                                  |
| Ferguson (37)                 | 2 x 234       | 4.68   | 0.2                             | 468                                    | 21.6   | 1.5                                  |
| Lancaster (52)<br>(no. 23-32) | 400 x 10      | 5.36   | 0.0025                          | 6.692                                  | 2.59   | 1.5                                  |

where  $m$  is the mean number of erythrocytes. In cases where the mean number counted is small, the distribution will be far from normal and the square root of the variance does not possess the usual characteristics of the S. D. for a normal distribution. What we are calling the observed S. D. of individual number per division is therefore not to be regarded as anything more than merely the observed square root of the variance. For a Poisson distribution, the observed square root of the variance will always equal  $\sqrt{m}$  or rather vary around  $\sqrt{m}$  no matter how small a number the mean  $m$  might be.

According to the models by E. Lancaster (32) Turner & Earl, Watanabe (86-87) the expected individual number per division be about 0.90  $\sqrt{m}$ . A similar result was observed by Berkson with their very careful technique. Engelhoff (30) and Lancaster counted numerous small deviations and the table it will be noticed (32) and Glatzel's (38) of deviations are only about theoretically expected value should be about observed density of cells.

Miller ocular disc is only  $1/9$ th of the area of the large division. Such methods are very timesaving when the percentage of reticulocytes is low. The number of erythrocytes counted in the small division, has to be multiplied with 9 in order to correspond to the reticulocytes encountered. This introduces a certain error the size of which depends entirely on the distribution of erythrocytes in a smear.

Schneidermann & Brecher (76) developed a formula for the standard deviation of an individual reticulocyte count, per-

formed with the Miller ocular disc. One of the assumptions upon which this formula was based, was the one that the total number of erythrocytes within one field of view of a smear follows the Poisson distribution. Schneidermann & Brecher (15 76) did not publish any observations regarding the distribution of total erythrocytes in a smear. We have also been unable to find any other publications regarding observed distribution error within one microscopic field of view of a smear.

## B Distribution of reticulocytes in blood smears

### 1 Theoretical distribution error

In an unfixed vitally-stained blood smear some of the erythrocytes will show granules or filaments. These erythrocytes are called reticulocytes and they are known to be juvenile red cells. These reticulocytes are usually given as a percentage of the total number of erythrocytes. A number ( $n$ ) of erythrocytes are counted, regardless of whether they contain a reticulum or not. During the counting one records the number ( $m$ ) of reticulocytes among the total number ( $n$ ) of erythrocytes, and

$\frac{m}{n} \cdot 100$  is the percentage of reticulocytes

Knowledge of the distribution of the reticulocytes among the non reticulocytes will have considerable interest, as such a knowledge will give us a way of calculating the standard deviation of an individual reticulocyte count. We will thus be able to know if a difference between two counts can be due to chance or not.

Reviewing the literature on the subject, we have only been able to find one mathematical model for the distribution of retu-

culocytes among the non-reticulocytes. This model is the concept that the reticulocytes are randomly mixed among the non-reticulocytes. During a count the chance of one erythrocyte being a reticulocyte can then be called  $p$  and the chance that it will not be a reticulocyte will be  $(1-p)$ . If random samples of  $n$  erythrocytes are examined, the frequencies of encountering 0 1 2 ...,  $n$  reticulocytes is given by the expansion of the binomial  $(p + q)^n$ . This distribution is therefore called the binomial distribution, or the Bernoulli distribution after the famous Swiss scientist who first found it. The variance of the binomial series is  $npq$ . When  $n$  is a large number the binomial distribution closely approaches the normal, and  $\sqrt{npq}$  can be taken to represent the standard deviation of an individual sample of  $n$ .

The reticulocytes are known to be more sticky (24 51) and to be larger and have a lower specific gravity (51) than the other erythrocytes. They might therefore conceivably clump together or sort themselves out during the staining or smearing pro-

cess, resulting in a distribution which is less uniform than a binomial distribution. Many authors have therefore applied the working hypothesis, that the reticulocytes in a smear are at the best randomly mixed among the non-reticulocytes (10 15 22 42, 50 61 76, 96)

Other authors think that the reticulocytes are more uniformly distributed than a binomial distribution (49 67). We think that such a working hypothesis could be acceptable, if we e.g. could assume some sort of repellent force which made each reticulocyte shun all other reticulocytes.

## 2 Observed distribution error

The reticulocytes were discovered by Erb (31) in 1865 and a more extensive description was given by Ehrlich (28) at a medical meeting in 1880. In the evaluation of different liver preparations in the treatment of pernicious anemia in the 1920ies and later reticulocyte counts have been extensively used. During the last decade, investigators of hematopoietic factors have also found the reticulocyte count to be a useful tool (17).

The observed standard deviations of individual reticulocyte counts have only rarely been published. In these few publi-

cations the S. D. has usually been calculated from a number of duplicate reticulocyte counts from the same sample or patient, or from a large number of counts of the same sample.

In table 2 are listed some exceptionally small observed standard deviations of individual reticulocyte counts, taken from the literature. One of the authors used rabbit's blood (49) the others human blood. From the table it will be noticed that all the authors have found standard deviations considerably below the value expected for a binomial distribution. Does this then mean that the reticulocytes in a blood smear are not randomly mixed but are more uniformly distributed among the non-reticulocytes? Or could it be that we are dealing with cases of unconscious bias again? In the work of Jacobsen, Plum & Rasch (49) published in 1947 proceedings were apparently taken to avoid unconscious bias, and the standard deviation still was much smaller than corresponding to a binomial distribution. Jacobsen *et al* (49) also attempted to produce photographic evidence for this uniform distribution. It was, however not quite clear whether the person identifying and marking the reticulocytes on the photographs, was completely unbiased (9).

Table 2 Observed S. D. of reticulocyte counts from the literature, compared to value expected with binomial distribution.

| Author              | Average no. of retics. per count | Average no. of eryths. per count | Obs. S. D. of indiv. retic. ct. (retics.) | Exp. S. D. binomial distrib. (retics.) | Obs. S. D. as fract. of Exp. S. D. |
|---------------------|----------------------------------|----------------------------------|---|--|------------------------------------|
| Peters & al (67)    | 113                              | 4 000                            | 5.96                                      | 10.4                                   | 0.57                               |
| Jacobsen & al. (49) | 100                              | 1 000                            | 3   | 9.49                                   | 0.32                               |
| Jacobsen & al. (49) | 300                              | 1 000                            | 3   | 13.81                                  | 0.19                               |
| Nordstrom (68)      | 37.2                             | 8 000                            | 1.68                                      | 6.68                                   | 0.28                               |
| Seip (78)           | 83                               | 5 000                            | 5.35                                      | 9.14                                   | 0.59                               |

## C Outline of present research problem

The randomness of the distribution of bacteria and yeast cells in a well mixed suspension, is widely appreciated.

When it comes to erythrocytes in a counting chamber the carefully done study of Berkson *et al* (3) shows the distribution to be slightly more uniform than a Poisson distribution. The cause of this deviation from Poisson distribution is thought to be due to the size of the erythrocytes, a sort of crowding effect.

Engbøll (30) Turner & Eadie (85) as well as Watanabe (86 87) tried to find a general formula describing the variability of randomly distributed equalized, non-overlapping discs. They approached the problem by assuming that there were a fixed number of available spaces for the discs, the number depending upon the area of the grid and the diameter of the discs. From this assumption they found an expression of the variability by assuming the observed number of erythrocytes to be randomly distributed in the available spaces. If their assumptions were right, the erythrocytes would truly be following the Bernoulli or binomial distributions. We think that their assumptions and model would fit the distribution of erythrocytes in a blood smear no worse than it would fit the distribution in a counting chamber.

We are not convinced however that this binomial model gives a really good description of a random distribution of discs although the model has proved adequate when tested for small disc densities.

1 The first of our two main parts will therefore be an attempt to find a mathematical expression for a random distribution of one set

of discs. And then attempting to find out if erythrocytes in a blood smear follow this distribution.

Reticulocytes are merely erythrocytes which show a reticulum after staining with a reticulocyte stain. When we perform an indirect reticulocyte count, a number ( $n$ ) of erythrocytes are counted, regardless of whether they contain a reticulum or not. During the counting we record the number ( $m$ ) of reticulocytes among the total number ( $n$ ) of erythrocytes. Some authors believe that the reticulocytes usually are randomly mixed among the non-reticulated erythrocytes (9 15 22 42, 50 62 76, 96). If the reticulocytes are not randomly mixed, these authors believe that the deviation will be towards less uniformity rather than more uniformity. These same authors therefore think that the error of a reticulocyte count will at the best be given by the standard deviation for a binomial or Bernoulli distribution.

Other authors just calculate their observed reticulocyte counting error and present it to their readers without commenting the fact that this error sometimes is only a fraction of the error expected for a binomial distribution (68 78).

A last group of authors frankly state that they can not a priori accept that the reticulocytes follow the binomial distribution, and that their observations are that the reticulocytes are much more uniformly distributed (49 67).

2. The second of our two main parts will therefore be an attempt to find a mathematical expression for the distribution of 2 sets of randomly placed and randomly mixed discs. And then, attempting to find out if reticulocytes in a smear follow this distribution.

## II One set of randomly placed individuals

### A Randomly placed points

#### 1 Previous work.

Before attempting to find a mathematical expression for randomly distributed discs, it will be useful to investigate randomly distributed points, in an attempt to find just where and how the disc distribution differs from the point distribution and thus obtain an expression for the random distribution of discs.

Poisson found the distribution which is named after him, and which describes the frequency of occurrence of rare events. These rare events may occur either in equal divisions of time or of space. Certain conditions are required in order that rare events shall follow the Poisson distribution. For one thing, the probability that one particular individual falls into one particular division has to be exceedingly small, and the probability of receiving the individual has to be the same for each division. The fact that an individual has fallen in a division must not affect the chances of other individuals falling into the division.

Abbe (1) theoretically calculated the variance for a red cell count to be equal to the number of cells counted, exactly the variance expected if the cells followed a Poisson distribution. Abbe did not himself have any observations to verify his theoretical calculations. A few years later

Lyon and Thomas (60) found the variance of their counts to come close to the counted number of cells, just like Abbe had expected.

Bortkiewicz (13) showed that the observed number of men killed from kicks of horses per army corps per year in Prussia during two decades towards the end of the last century followed the Poisson distribution. In this example regarding deaths of horse-kick per army corps per year we are dealing with rare events occurring in divisions of time.

In 1907 "Student" (83) observed that a well mixed suspension of yeast cells placed in a haemocytometer under ideal conditions would follow the Poisson distribution. In this example we are dealing with rare events occurring in divisions of space.

The occurrences of several other events have since then been found to follow the Poisson distribution more or less closely. Ebenhart & Wilson (29) have listed the following: Emission of alpha particles from polonium per division of time; number of umbrellas left on buses (statistical control, eliminate rainy days); death notices for men over 85 in the obituary column of London Times; wrong number connections in a telephone exchange; number of fires in New York City during a year (statistical control, eliminate July 4th and

Election day) defects in a manufactured article, calls for a reference book in a university library, counts of bacteria in counting chambers and counts of bacterial colonies on plates.

In all the previous works we have encountered, the observed distribution has been assessed by counting the number of individuals in the divisions of time or of space, and then comparing the occurrences with those expected for a Poisson distribution. The expected frequencies of occurrences for the Poisson distribution are calculated from  $\lambda e^{-\lambda} (1 + \lambda + \frac{\lambda^2}{2!} + \frac{\lambda^3}{3!} + \dots)$

where  $\lambda$  is the number of divisions and  $m$  the observed mean number of individuals per division. The variance of a Poisson distribution is also equal to the mean  $m$ . When  $m$  has a large value the distribution of numbers approximates closely to the normal form, and  $\sqrt{m}$  can be taken to represent the standard deviation of the number of individuals per division.

We believed that the distance from one individual to the closest neighbor might be useful in the investigation of random distributions, but were unable to find any previous work on the subject.

## 2 Own work on models

### a) Theoretically calculated mean free area.

We should like to obtain an expression of the distance from one individual to the closest neighbor for a perfect Poisson distribution. Such a perfect Poisson distribution would e.g. be if points were randomly placed over a plane area. Knowledge of the distance to the closest neighbor for a random distribution of  $n$  points, might give us a way of calculating the expected distribution for  $n$  discs with a given diameter. One of the differences between the two distributions is that the distance

from one disc center to the center of the closest neighbor can never be smaller than one disc diameter provided there be no over-lapping.

It is more convenient to work with the mean free area in stead of mean distance to the closest neighbor. The mean free area is merely the mean of the area enclosed within a circle with radius equal to the distance to closest neighbor. A circle drawn around each point and through the closest neighbor point thus encloses the free area around the point.

Assume a number ( $n$ ) of points randomly placed in a certain area ( $A$ ). If the area  $A$  is divided into just as many divisions as there are number of points, the mean number of points per division will be 1. If we draw equal sized circles of an area  $\frac{A}{n}$  around each randomly placed point, the expected mean number of points inside the circle will also be 1 (disregarding the point in the center of each circle).

If we draw large, equal circles e.g. with an area of  $\frac{94}{n-1}$  around each point, the expected mean number of points enclosed will be 1 (still disregarding the point in the center). The number of points enclosed within these circles will follow the Poisson distribution, and the frequency of circles containing 0, 1, 2, 3, ... individuals will be given by the terms of the exponential

$$\lambda^{-n} (1 + \lambda + \frac{\lambda^2}{2!} + \frac{\lambda^3}{3!} + \dots)$$

where  $\lambda$  is the number of circles,  $m$  the mean number of individuals per circle, and  $x$  = factorial  $x$ . Assume having 100 circles each with an area of  $\frac{94}{n-1}$  drawn

around 100 randomly placed points. We shall then expect 0.01 circles to contain 11 points, 0.1 to have 1 point, 0.5 to have

2 points, 1.5 to have 3 points etc. The highest expected frequency will be 13.2 equally high for groups with 8 and 9 points enclosed. The frequency will then diminish as the number of points enclosed increases. For the group with 21 points enclosed, the frequency will thus be only 0.03

We shall now consider each of the frequency groups separately. Essentially no circles contain 0 points. Only 0.1 circle out of 100 is expected to contain 1 point. Circles which do contain 1 point, may have this point located anywhere inside the  $\frac{9A}{\pi-1}$  large circle. The free area around the circle center will accordingly take any

value from 0 to  $\frac{9A}{\pi-1}$  and  $\frac{9}{2} \frac{A}{\pi-1}$  will be the average for that frequency group.

For the frequency group with 2 points, probability calculations show that the average free area is  $\frac{9}{3} \frac{A}{\pi-1}$ . For frequency

groups with a number ( $p$ ) of points, the average free area will be  $\frac{9}{p+1} \frac{A}{\pi-1}$ .

The frequency of each group is then multiplied with the average free area for that frequency group. The sum of all the (frequencies multiplied with the respective average free area) will give us the sum of all the free areas around the 100 randomly distributed points. It is evident that the frequency of each group ( $p$ ) is multiplied with  $\frac{1}{p+1} \times \frac{A}{\pi-1}$   $m$  being the mean number ( $9$ ) of points, and  $p$  the number of points for that particular frequency group.

If we multiply  $\frac{1}{p+1}$  into the frequency

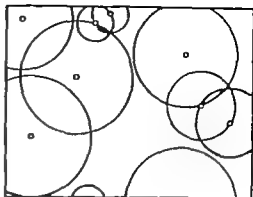


Fig. 3 Free areas around randomly distributed points. Mean free area is about  $\frac{A}{\pi-1}$

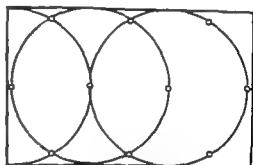


Fig. 4 Free areas around uniformly arranged points. There is much overlapping, and mean free area is much more than  $\frac{A}{\pi-1}$

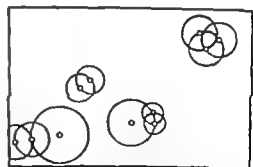


Fig. 5. Free area around points less uniformly arranged than random distributions. Mean free area is less than  $\frac{A}{\pi-1}$



Table 5. Model V.k. Points plotted from random number pairs page V &amp; VI line 6 to line 13 on millimeter sheet 30 cm x 30 cm.

|  | Right half            | Left half             |
|--|-----------------------|-----------------------|
| Area of each half sheet ( $A$ )              | 364.5 cm <sup>2</sup> | 364.5 cm <sup>2</sup> |
| True number of points per half sheet ( $n$ ) | 125                   | 125                   |
| Expected mean free area ( $\frac{A}{n-1}$ )  | 2.940 cm              | 2.940 cm              |
| Observed mean free area                      | 2.854 cm              | 2.890 cm              |
| Observed S. D. of individual free areas      | 2.69 cm               | 2.63 cm <sup>2</sup>  |
| Observed number of points                    | 124                   | 126                   |

Table 6. Model V.m. Points plotted from random number pairs page V &amp; VI line 19 to line 25 on millimeter sheet 30 cm x 30 cm.

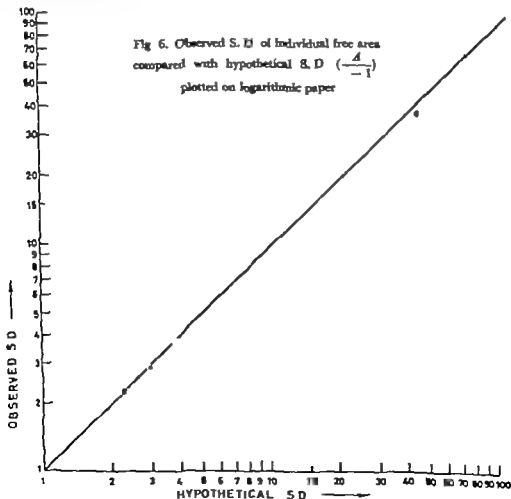
|  | Right half            | Left half             |
|--|-----------------------|-----------------------|
| Area of each half sheet ( $A$ )              | 364.5 cm              | 364.5 cm <sup>2</sup> |
| True number of points per half sheet ( $n$ ) | 99.5                  | 99.5                  |
| Expected mean free area ( $\frac{A}{n-1}$ )  | 3.701 cm              | 3.701 cm <sup>2</sup> |
| Observed mean free area                      | 4.026 cm <sup>2</sup> | 3.900 cm              |
| Observed S. D. of individual free areas      | 3.78 cm <sup>2</sup>  | 4.14 cm               |
| Observed number of points                    | 103                   | 96                    |

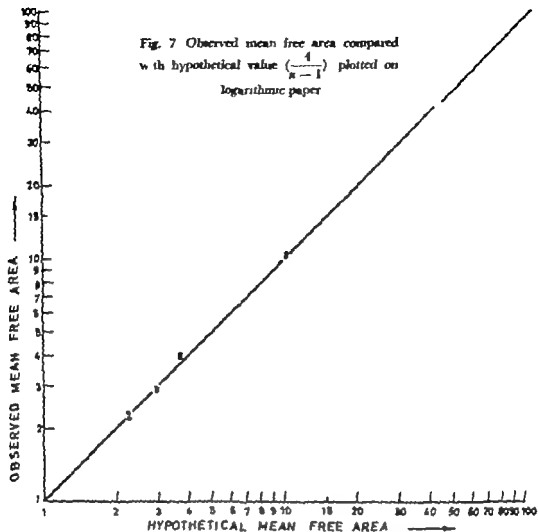
Table 7. Model L. Points plotted from random number pairs page V &amp; VI line 14 to line 18 on millimeter sheet 50 cm x 50 cm.

|  | Right half | Left half             |
|--|------------|-----------------------|
| Area of each half sheet ( $A$ )              | 1012.5 cm  | 1012.5 cm             |
| True number of points per half sheet ( $n$ ) | 100        | 100                   |
| Expected mean free area ( $\frac{A}{n-1}$ )  | 10.230 cm  | 10.230 cm             |
| Observed mean free area                      | 10.26 cm   | 10.33 cm <sup>2</sup> |
| Observed S. D. of individual free areas      | 9.03 cm    | 11.04 cm <sup>2</sup> |
| Observed number of points                    | 107        | 93                    |

Table 8. Model No. Points plotted from random number pairs page V & VI line 26 to line 30 on millimeter sheet 100 cm x 100 cm.

|  | Right half              | Left half               |
|--|-------------------------|-------------------------|
| Area of each half sheet ( $A$ )                    | 4,512.5 cm <sup>2</sup> | 4,512.5 cm <sup>2</sup> |
| True number of points per half sheet ( $\lambda$ ) | 108.5                   | 108.5                   |
| Expected mean free area ( $\frac{A}{\lambda}$ )    | 41.98 cm <sup>2</sup>   | 41.98 cm <sup>2</sup>   |
| Observed mean free area                            | 41.19 cm <sup>2</sup>   | 47.74 cm <sup>2</sup>   |
| Observed S. D. of individual free areas            | 37.67 cm                | 37.27 cm                |
| Observed number of points                          | 117                     | 100                     |





c. Observed mean free area compared to theoretical value

If innumerable sheets of millimeter paper contained randomly placed points from the same very large population, the observed number of points per half sheet would vary around the true mean number  $n$  per half sheet. According to our theoretical calculations the observed mean free area would similarly vary around  $\frac{4}{n-1}$ .

When we are plotting random points on each sheet until we have  $2 \times n$  points, the true number per half sheet will always be  $n$ . This true mean number ( $n$ ) is therefore used for calculating the expected mean free area from our formula  $\frac{4}{n-1}$ .

We should like to know whether the difference between observed and expected mean free areas is significant. We would expect that the observed S. D. of individual

free areas would tend to vary in the same direction as the mean free area. If we would calculate the standard deviation of the observed mean free area from the

formula  $\frac{\text{Observed S D indiv}}{\sqrt{\text{Observed no}}}$  this value

would also be expected to vary in the same direction as the observed mean free area. The standard deviation of the observed mean free area would in that case not be an appropriate measure of the difference between our hypothesis and the observed mean free area.

Tables 4—8 and fig 7 show the observed mean free areas to be scattered around the expected values, sometimes slightly above, sometimes slightly below. If we accept that the expected S D of the mean free area will be in the neighbor

hood of  $\frac{A}{(-1)\sqrt{n}}$ , the difference be

tween observed and expected mean free area is in no case as large as 2 of these expected standard deviations.

### 3 Conclusions

1 We found theoretically the mean free area of a random distribution of points to

be  $\frac{A}{n-1}$  where  $A$  is the total area and  $n$  is the number of points. For points more uniformly distributed, the mean free area

will be greater than  $\frac{A}{n-1}$ . For distributions less uniform than a random distribution the mean free area will be smaller than  $\frac{A}{n-1}$ .

2 Tests on 5 models of randomly distributed points on sheets of millimeter paper showed the observed values for mean free area to agree well with the theoretically calculated values ( $\frac{A}{n-1}$ ).

3. Observations on 5 models of randomly distributed points on sheets of millimeter paper showed the standard deviation of individual free areas to come very close to  $\frac{A}{n-1}$  ( $A$  still being the total area and  $n$  the number of points).

## B Randomly placed discs

### 1 Previous work.

We have only been able to find five publications concerning the theoretical development of a random distribution of equalized, non-overlapping discs (30, 43 85 86 87). The formulae of Engbaff (30) Turner & Eadie (85) Hamaker (43) and Watanabe (86 87) were all based on the assumption that the non-overlapping discs occupied randomly some of a limited number of available spaces. Each division

would have a number  $n$  of available spaces, a random number of these being occupied by discs. The variance of number of discs in a division could accordingly be derived from the variance of a binomial distribution

$$\text{Variance} = p q n,$$

where  $p$  was the chance that an available space was occupied by a disc,  $q$  the chance that it was not occupied and  $n$  the number of available spaces. The formulae for

the variance of a random distribution of discs, were in no cases tested on randomly placed, equalized non-overlapping discs. They were only tested on erythrocytes distributed on the bottom of a counting chamber. The density of individuals during these tests was always rather low and the formulae have accordingly never been tested at maximal or near maximal, disc or erythrocyte densities.

We believed that the distance from one disc center to the center of the closest neighbor might be useful in the investigation of random distributions, but were unable to find any previous work on the subject.

## 2 Own work on models

### a) Hypothesis for mean variable free area.

The first step must be to obtain an expression of the distance from the center of one individual to the center of the closest neighbor for a perfectly random distribution of equalized, non-overlapping discs. Such an expression will be a step towards finding the formula for a random distribution of discs.

Our term free area around a point or around a disc center is already defined. Provided there is no overlapping of discs, no free area around a disc center can be smaller than (disc diameter). Subtracting this innermost, non-variable area from the free area around the disc center gives us what we shall call the *variable free area*. See fig. 8.

For a random distribution of points the mean free area can be taken as an expression of the amount of room each point has to vary over. For random distributions of discs the *mean variable free area* similarly expresses the amount of room the disc has to vary over.

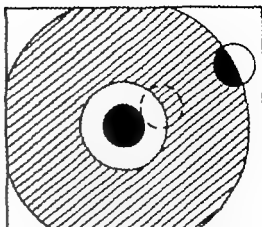


Fig. 8. Variable free area around central disc is shaded. Room-occupying structures enclosed within the free area around center of disc, in black.

The mean free area for a random distribution of points was shown to be  $\frac{A}{n-1}$

where  $A$  was total area and  $n$  number of points. When we on the other hand are dealing with random disc distributions, the situation is slightly different. The difference is due to the fact that the circle drawn around each disc center and through the closest neighboring center will be enclosing some room-occupying structures. See fig. 8. These structures are one whole disc, namely the one around whose center the circle is drawn and also a portion of the closest neighboring disc. (We are disregarding any 2nd or 3rd closest neighbor discs, portions of which might possibly also be inside of the circle.) The portion cut off the closest neighboring disc, will vary slightly with the distance between the two disc centers.

Preliminary investigation led us to the hypothesis that the mean variable free area is  $\frac{A}{n-1}$  minus (structures enclosed within mean free area)

b) *Observed S D of individual variable free area.*

Nine models of randomly distributed disc centers were constructed on sheets of millimeter paper. We used the same grid system as for plotting randomly distributed points. The disc radius was to be 8 millimeters, and circles with a radius of exactly

16 millimeters were therefore drawn around the center of each millimeter square which was picked. If a later random number pair indicated a millimeter square inside of a previously drawn circle this square was omitted. There could accordingly never be any overlapping of discs.

The border zone of each sheet of millimeter paper was always omitted. One of

Table 9 Distance to closest neighbor in 9 models of randomly distributed discs.  
Unit is 1 millimeter

| Distance                | Model Gg |                        |      |                        | Model Ec |                        |      |                        | Model Fl       |                        |      |                        |
|-------------------------|----------|------------------------|------|------------------------|----------|------------------------|------|------------------------|----------------|------------------------|------|------------------------|
|                         | Right    |                        | Left |                        | Right    |                        | Left |                        | Right          |                        | Left |                        |
|                         | No.      | Var free area<br>× No. | No.  | Var free area<br>× No. | No.      | Var free area<br>× No. | No.  | Var free area<br>× No. | No.            | Var free area<br>× No. | No.  | Var free area<br>× No. |
| 16                      | 17       |                        | 24   |                        | 11       |                        | 6    |                        | 7 <sup>1</sup> |                        | 6    |                        |
| 17                      | 19       | 1,972                  | 33   | 3,426                  | 18       | 1,868                  | 18   | 1,868                  | 6              | 622.9                  | 7    | 726.6                  |
| 18                      | 18       | 3,834                  | 13   | 2,769                  | 12       | 2,357                  | 8    | 1,704                  | 7              | 1,491                  | 8    | 1,704                  |
| 19                      | 23       | 7,590                  | 23   | 7,590                  | 2        | 660                    | 4    | 1,320                  | 5              | 1,650                  | 5    | 1,650                  |
| 20                      | 12       | 5,437                  | 12   | 5,437                  | 2        | 903.9                  | 4    | 1,812                  |                |                        | 1    | 433                    |
| 21                      | 20       | 11,630                 | 6    | 3,492                  | 4        | 2,328                  | 2    | 1,163                  | 2              | 1,163                  | 1    | 362                    |
| 22                      | 8        | 5,728                  | 9    | 6,443                  | 5        | 3,580                  | 8    | 5,728                  |                |                        |      |                        |
| 23                      | 5        | 4,290                  | 6    | 5,148                  | 5        | 4,290                  | 1    | 838                    |                |                        |      |                        |
| 24                      | 11       | 11,060                 | 3    | 3,015                  | 2        | 2,010                  | 2    | 2,010                  | 1              | 1,005                  | 1    | 1,005                  |
| 25                      | 2        | 2,317                  | 8    | 5,794                  |          |                        |      |                        |                |                        |      |                        |
| 26                      | 1        | 1,319                  | 5    | 6,597                  |          |                        |      |                        |                |                        |      |                        |
| 27                      | 1        | 1,486                  | 2    | 2,972                  |          |                        |      |                        |                |                        | 1    | 1,486                  |
| 28                      |          |                        | 3    | 4,974                  |          |                        |      |                        |                |                        |      |                        |
| 29                      |          |                        |      |                        |          |                        |      |                        |                |                        |      |                        |
| 30                      | 1        | 2,023                  |      |                        |          |                        |      |                        |                |                        |      |                        |
| Total no.               | 158      |                        | 144  |                        | 61       |                        | 53   |                        | 28             |                        | 30   |                        |
| Total var free area     |          | 58,686                 |      | 57,657                 |          | 18,198.9               |      | 16,463                 |                | 5,931.9                |      | 7,608.6                |
| Obs. mean var free area |          | 425.3                  |      | 400.4                  |          | 298.3                  |      | 310.6                  |                | 211.9                  |      | 253.6                  |

Table 10. Model II. Disc centers plotted from random number pairs page V & VI 1 to line 5 on millimeter sheet 100 cm  $\times$  100 cm.

|   | Right half              | Left half               |
|---|-------------------------|-------------------------|
| Area of each half sheet ( $A$ )   | 4,512.5 cm <sup>2</sup> | 4,512.5 cm <sup>2</sup> |
| True number of discs per half sheet ( $n$ )   | 100.5                   | 100.5                   |
| Area of each disc ( $D$ )   | 2.01 cm <sup>2</sup>    | 2.01 cm <sup>2</sup>    |
| Hypothetical mean variable free area ( $\frac{A}{n-1}$<br>minus 1.46 $\times$ $D$ ) | 42.42 cm                | 42.42 cm                |
| Observed mean variable free area  | 47.51 cm <sup>2</sup>   | 36.47 cm <sup>2</sup>   |
| Observed S. D. of individual var free area  | 46.48 cm <sup>2</sup>   | 33.9 cm <sup>2</sup>    |
| Observed number of discs  | 93                      | 108                     |

Table 11. Model Cc. Disc centers plotted from random number pairs page I & II line 22 to line 31 on millimeter sheet 100 cm  $\times$  100 cm.

|   | Right half              | Left half               |
|---|-------------------------|-------------------------|
| Area of each half sheet ( $A$ )   | 4,512.5 cm <sup>2</sup> | 4,512.5 cm <sup>2</sup> |
| True number of discs per half sheet ( $n$ )   | 183.5                   | 183.5                   |
| Area of each disc ( $D$ )   | 2.01 cm                 | 2.01 cm <sup>2</sup>    |
| Hypothetical mean variable free area ( $\frac{A}{n-1}$<br>minus 1.46 $\times$ $D$ ) | 21.79 cm                | 21.79 cm                |
| Observed mean variable free area  | 21.14 cm                | 19.51 cm                |
| Observed S. D. of individual var free area  | 22.56 cm <sup>2</sup>   | 18.96 cm <sup>2</sup>   |
| Observed number of discs  | 185                     | 182                     |

Table 12. Model Dd. Disc centers plotted from random number pairs page I & II line 32 to line 42 on millimeter sheet 100 cm  $\times$  100 cm.

|   | Right half            | Left half             |
|---|-----------------------|-----------------------|
| Area of each half sheet ( $A$ )   | 4,050 cm <sup>2</sup> | 4,050 cm <sup>2</sup> |
| True number of discs per half sheet ( $n$ )   | 242                   | 242                   |
| Area of each disc ( $D$ )   | 2.01 cm               | 2.01 cm               |
| Hypothetical mean variable free area ( $\frac{A}{n-1}$<br>minus 1.46 $\times$ $D$ ) | 13.87 cm <sup>2</sup> | 13.87 cm              |
| Observed mean variable free area  | 13.80 cm <sup>2</sup> | 14.15 cm <sup>2</sup> |
| Observed S. D. of individual var free area  | 11.43 cm              | 12.36 cm              |
| Observed number of discs  | 46                    | 238                   |

Table 13 Model Hh. Disc centers plotted from random number pairs page III & IV line 42 to line 48 on millimeter sheet 50 cm x 50 cm.

|  | Right half              | Left half               |
|--|-------------------------|-------------------------|
| Area of each half sheet (A)  | 1,012.5 cm <sup>2</sup> | 1,012.5 cm <sup>2</sup> |
| True number of discs per half sheet ( )                                  | 87.5                    | 87.5                    |
| Area of each disc (D)  | 2.01 cm <sup>2</sup>    | 2.01 cm <sup>2</sup>    |
| Hypothetical mean variable free area ( $\frac{A}{-1}$<br>minus 1.46 x D) | 8.77 cm <sup>2</sup>    | 8.77 cm <sup>2</sup>    |
| Observed mean variable free area   | 10.61 cm <sup>2</sup>   | 8.632 cm <sup>2</sup>   |
| Observed S. D. of individual var free area                               | 10.09 cm <sup>2</sup>   | 7.41 cm <sup>2</sup>    |
| Observed number of discs   | 89                      | 86                      |

Table 14 Model Aa. Disc centers plotted from random number pairs page I & II line 11 to line 21 on millimeter sheet 50 cm x 50 cm.

|  | Right half              | Left half               |
|--|-------------------------|-------------------------|
| Area of each half sheet (A)  | 1,012.5 cm <sup>2</sup> | 1,012.5 cm <sup>2</sup> |
| True number of discs per half sheet ( )                                  | 113.5                   | 113.5                   |
| Area of each disc (D)  | 2.01 cm <sup>2</sup>    | 2.01 cm <sup>2</sup>    |
| Hypothetical mean variable free area ( $\frac{A}{-1}$<br>minus 1.46 x D) | 6.07 cm <sup>2</sup>    | 6.07 cm <sup>2</sup>    |
| Observed mean variable free area   | 6.748 cm <sup>2</sup>   | 5.228 cm <sup>2</sup>   |
| Observed S. D. of individual var free area                               | 5.59 cm                 | 4.74 cm                 |
| Observed number of discs   | 109                     | 118                     |

Table 15. Model Gg. Disc centers plotted from random number pairs page III & IV line 27 to line 41 on millimeter sheet 50 cm x 50 cm.

|  | Right half              | Left half               |
|--|-------------------------|-------------------------|
| Area of each half sheet (A)  | 1,012.5 cm <sup>2</sup> | 1,012.5 cm <sup>2</sup> |
| True number of discs per half sheet ( )                                  | 141                     | 141                     |
| Area of each disc (D)  | 2.01 cm <sup>2</sup>    | 2.01 cm <sup>2</sup>    |
| Hypothetical mean variable free area ( $\frac{A}{-1}$<br>minus 1.46 x D) | 4.50 cm                 | 4.50 cm                 |
| Observed mean variable free area   | 4.53 cm <sup>2</sup>    | 4.004 cm <sup>2</sup>   |
| Observed S. D. of individual var free area                               | 3.55 cm <sup>2</sup>    | 4.17 cm <sup>2</sup>    |
| Observed number of discs   | 158                     | 144                     |



Table 10. Model II. Disc centers plotted from random number pairs page V & VI 1 to line 5 on millimeter sheet 100 cm  $\times$  100 cm.

|  | Right half              | Left half               |
|--|-------------------------|-------------------------|
| Area of each half sheet (A)  | 4,512.5 cm <sup>2</sup> | 4,512.5 cm <sup>2</sup> |
| True number of discs per half sheet ( )  | 100.5                   | 100.5                   |
| Area of each disc (D)  | 2.01 cm <sup>2</sup>    | 2.01 cm <sup>2</sup>    |
| Hypothetical mean variable free area ( $\frac{A}{n-1}$<br>minus 1.46 $\times$ D) | 42.47 cm <sup>2</sup>   | 42.42 cm <sup>2</sup>   |
| Observed mean variable free area   | 47.51 cm <sup>2</sup>   | 36.47 cm <sup>2</sup>   |
| Observed S. D. of individual var free area                                       | 46.48 cm <sup>2</sup>   | 33.9 cm <sup>2</sup>    |
| Observed number of discs   | 93                      | 108                     |

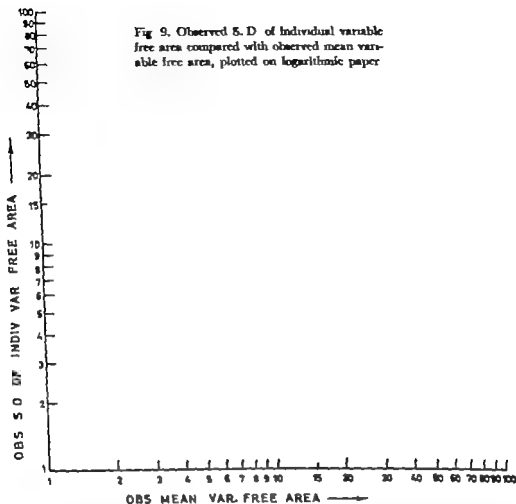
Table 11 Model Cc. Disc centers plotted from random number pairs page I & II line 22 to line 31 on millimeter sheet 100 cm  $\times$  100 cm.

|  | Right half              | Left half               |
|--|-------------------------|-------------------------|
| Area of each half sheet (A)  | 4,512.5 cm <sup>2</sup> | 4,512.5 cm <sup>2</sup> |
| True number of discs per half sheet (n)  | 183.5                   | 183.5                   |
| Area of each disc (D)  | 2.01 cm <sup>2</sup>    | 2.01 cm <sup>2</sup>    |
| Hypothetical mean variable free area ( $\frac{A}{n-1}$<br>minus 1.46 $\times$ D) | 21.79 cm <sup>2</sup>   | 21.79 cm <sup>2</sup>   |
| Observed mean variable free area   | 21.14 cm <sup>2</sup>   | 19.51 cm <sup>2</sup>   |
| Observed S. D. of individual var free area                                       | 22.56 cm <sup>2</sup>   | 18.96 cm <sup>2</sup>   |
| Observed number of discs   | 185                     | 182                     |

Table 12 Model Dd. Disc centers plotted from random number pairs page I & II line 32 to line 42 on millimeter sheet 100 cm  $\times$  100 cm.

|  | Right half            | Left half             |
|--|-----------------------|-----------------------|
| Area of each half sheet (A)  | 4,050 cm <sup>2</sup> | 4,050 cm <sup>2</sup> |
| True number of discs per half sheet ( )  | 242                   | 242                   |
| Area of each disc (D)  | 2.01 cm <sup>2</sup>  | 2.01 cm <sup>2</sup>  |
| Hypothetical mean variable free area ( $\frac{A}{n-1}$<br>minus 1.46 $\times$ D) | 13.87 cm <sup>2</sup> | 13.87 cm <sup>2</sup> |
| Observed mean variable free area   | 13.80 cm <sup>2</sup> | 14.15 cm <sup>2</sup> |
| Observed S. D. of individual var free area                                       | 11.43 cm <sup>2</sup> | 12.36 cm <sup>2</sup> |
| Observed number of discs   | 46                    | 238                   |

Fig 9. Observed S. D of individual variable free area compared with observed mean variable free area, plotted on logarithmic paper

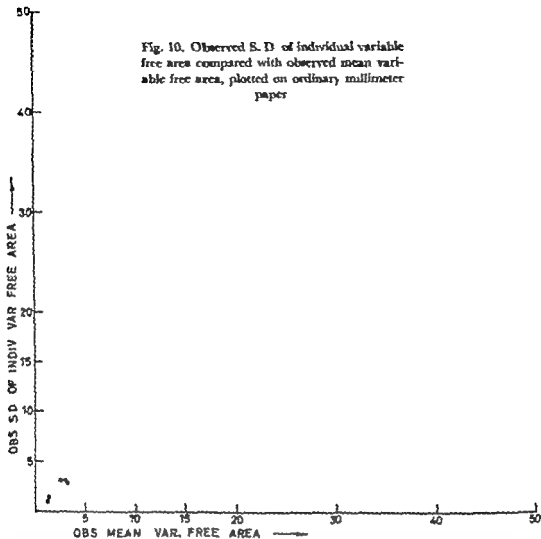


the reasons was that the disc centers in that zone did not have neighbors on all sides. Another reason was that models with a high density of disc centers would have a relative increase in disc centers in the border zone. The reason for this is obvious. A division in the middle of the sheet might be partially blocked by circles with their center either on the left or on the right side of the division. A division along the left border on the other hand,

could only be blocked by circles with their center on the right side. Divisions lying in the border zone would therefore usually contain more disc centers than would other divisions.

Each sheet of millimeter paper was divided by a midline into left and a right half. All the discs in one half of the sheet were considered as one sample. For all disc centers in each sample we measured the distance ( $r$ ) to the closest neigh-

Fig. 10. Observed S. D. of individual variable free area compared with observed mean variable free area, plotted on ordinary millimeter paper

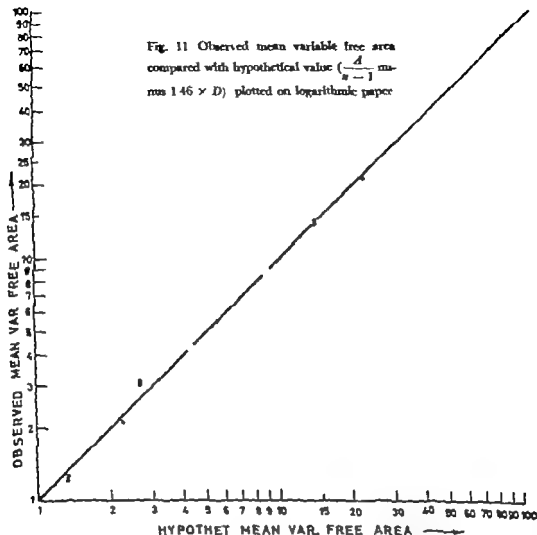


boring disc center and calculated the observed free area  $\pi r^2$ . From the observed free area  $\pi r^2$  we subtracted the innermost circular portion with a radius of 1.6 cm and area of 8.04 cm<sup>2</sup> thus obtaining the observed variable free area, table 9. The S. D. (only in the mean ng square root of the variance) of the observed individual variable free area for each half sheet was calculated. From tables 10—18 and figures 11 and 10 it is seen that the observed S. D. of individual variable free area

tended to vary in the same direction as the observed mean variable free area.

The value of the observed S. D. of individual variable free area was generally found to be slightly smaller than the observed mean variable free area. Figures 9 and 10 suggest that the correlation might be a linear one, figure 10 suggesting that the observed S. D. is slightly more than 90 per cent of the value of the observed mean variable free area.

Fig. 11 Observed mean variable free area compared with hypothetical value ( $\frac{A}{n-1}$  minus  $146 \times D$ ) plotted on logarithmic paper



c) *Observed mean variable free area compared to hypothetical value*

If sheets of millimeter paper were taken from the same very large population, the observed number of points per half sheet would vary around the true mean number ( $\bar{x}$ ) per half sheet. When we are plotting randomly distributed discs on each sheet until we have  $2n$  points, the true number per half sheet will always be  $n$ . This true

number ( $\bar{x}$ ) was therefore used for calculating the hypothetical mean variable free area from the formula  $\frac{A}{n-1}$  minus (structures enclosed within mean free area). The size of the structures enclosed within mean free area varies slightly with the mean free area itself. As the mean distance to the center of the closest neighbor increases from a minimum of 16 millimeters towards unlimited values, the portion cut

off the closest neighbor varies from 45.0 to 47.9 on the average 46 per cent. In our formula for calculating the hypothetical mean variable free area we have in all the cases used 46 per cent to represent the portion cut off the closest neighbor.

Tables 10—18 and fig. 11 show the observed mean variable free areas to be scattered around the hypothetical values, sometimes a little above, sometimes a little below. We should like to know whether the difference between observed and hypothetical mean variable free area is significant.

From tables 10—18 and figures 9 and 10 it is seen that the observed S. D. of individual variable free area tended to vary in the same direction as the mean free area. If we would calculate the standard deviation of the observed mean variable free area from the formula given on page 32 this value would also be expected to vary in the same direction as the observed mean variable free area. The standard deviation of the observed mean variable free area would therefore not be an appropriate measure of the difference between our hypothesis and the observed mean variable free area.

In such cases where the group mean and the standard deviations tend to be proportional the data may sometimes be transformed to logarithms before making statistical significance test. We did not however undertake this procedure.

Instead of such a transformation we tried to calculate an approximate value for expected S. D. of the hypothetical mean variable free area. From figures 9 and 10 a linear correlation was suggested between observed mean variable free area and observed S. D. of individual variable free area, the latter being in the neighborhood of 80 per cent of the former. If we therefore will use the figure 90 per cent

we may calculate the expected S. D. of a hypothetical mean variable free area to be

$$\left( \frac{A}{n-1} \text{ minus } 1.46 \times D \right) \times \frac{9}{10} \times \frac{1}{\sqrt{n}}$$

In 1 case the observed mean variable free area departs 2.18 of these expected standard deviations, from the hypothetical value. In the other 17 cases the departures from the hypothetical value, are less than 2 of these standard deviations.

We also calculated the hypothetical mean variable free areas using a more exact percentage, in stead of 146 per cent of one disc in all cases. The difference from the observed values remained practically unchanged.

d) *Observed mean variable free area for disc distributions more uniform, and less uniform, than random ones*

On page 30 we referred to fig. 3—5 and shortly stated, that points more uniformly distributed have a mean free area greater than do randomly distributed points. In a similar way disc centers more uniformly distributed will have a mean free area greater than the centers of randomly distributed, non-overlapping discs.

When it comes to disc distributions, it is the mean variable free area which has received most of our interest. We find that disc centers more uniformly distributed will have a mean variable free area greater than the centers of randomly distributed non-overlapping discs.

As an example we shall assume having discs with 0.8 cm radius randomly distributed over an area of 100 cm<sup>2</sup> until there is no space available, provided there be no overlapping. According to our experiment *Typ* in table III around 24.3 randomly placed discs will be needed to fill such an area. If the same size of discs are packed in the most compact, triangular arrangement

(fig. 2) about 45.3 discs will be needed to fill the same area. Assume keeping the uniform, triangular arrangement of the disc centers, but spacing the discs to give exactly 24.3 individuals per 100 cm<sup>2</sup>. The variable free area around each disc center has become unvariable, each being equal to the mean, which is 6.9 cm<sup>2</sup>. As a comparison for 24.3 randomly distributed discs over the same area, the mean variable free area is about 1.3 cm<sup>2</sup>.

Discs less uniformly distributed than a random disc distribution, will be placed in clusters here and there, and the mean variable free area will thus be smaller.

We shall now leave the random distribution of discs, and study discs packed into the 100 cm<sup>2</sup> area with the most compact triangular arrangement (fig. 2). The maximal number in this area is 45.3 discs provided the radius still is 0.8 cm., and there is no overlapping. With this most compact arrangement each disc is touching 6 neighbors. The free area around each disc center is 8.04 cm<sup>2</sup> and the mean free area is the same. The variable free area has become unvariable and is zero.

This arrangement of disc centers is completely uniform, and yet, if one places a grid randomly over the discs, the number of individuals will vary from one division of the grid to another. We performed some experiments with coins glued to a cardboard in the most compact, triangular arrangement. A perfectly quadratric window was cut out of a washed roentgen film. The roentgen film was then randomly placed 100 times over the coins. Each time the number of individuals appearing in the window was recorded using a similar technique as for counting erythrocytes in a counting chamber. The standard deviation of an individual count was calculated in the usual manner. We made a series of experiments, varying the size of

the window from one experiment to the other. For the largest window the mean number of coins appearing was about 56. For the smallest window the mean number of coins was about 7. The observed S. D. was for some division sizes as low as 0.10 times the S. D. of Poisson distribution with the same mean. For other division sizes the observed S. D. was as high as 0.28 times the S. D. of a Poisson distribution.

c) *Size of divisions influencing the variance of counts in equal divisions.*

Student<sup>10</sup> (84) maintained that a distribution of randomly placed discs would be more uniform than the Poisson distribution. Berkson *et al* (5) counted erythrocytes in 400 divisions each 1/400 mm<sup>2</sup> and found a standard deviation of 0.92 times that expected for a Poisson distribution with the same mean. Lancaster (52) by geometrical considerations concluded that the deviation from the Poisson distribution would be smaller if the erythrocytes were counted in large divisions in the counting chamber. Lancaster assumed that all the erythrocytes would land on the bottom of the counting chamber in the Poisson distribution. If one cell happened to fall on top of another then the top cell would slide off along the line of centers until the two were just in contact. If this is what happens in a counting chamber Lancaster's conclusions probably are correct. But he has given no proof of his assumptions. And he has not offered any observations to support the theoretical conclusion that the deviation from the Poisson distribution is smaller if the erythrocytes are counted in larger divisions.

In our experimental work with randomly distributed discs on sheets of millimeter paper we also believed that the size of the divisions would influence the S. D. of an

individual count. On our models however the influence was thought to be in the opposite direction to what Lancaster found by his geometrical considerations for the chamber situation.

The S. D. of counts of randomly distributed discs is a certain fraction of the S. D. of a Poisson distribution with the same mean ( $m$ ). We thought that the percentage deviation from the S. D. of a Poisson distribution would increase with increased size of the divisions. The reason for this seemed fairly obvious to us. In the small divisions all or almost all disc centers lie in the border zone of the divisions, whereas in large divisions only a few lie in that zone. If one division happens to contain many disc centers, disc centers located in the border zone of the division will block parts of the neighbor divisions. These neighbor divisions might therefore obtain an abnormally low number of disc centers. Thus blocking of neighbor divisions will be of less importance when divisions are large with relatively fewer disc centers in the border zone of the division.

In table 19 we compared the observed S. D. when the same discs randomly distributed over an area were counted in divisions of different size. The S. D. was each time expressed as a fraction of the S. D. expected for a Poisson distribution with the same mean number per division. The percentage deviation from the S. D. of a Poisson distribution is seen to increase with increased size of the divisions, exactly as was expected.

We have thus far looked into the influence of the division size upon the S. D. of an individual count, the S. D. being calculated from multiple counts of the same sample by the usual formula (p. 30).

Sometimes we assess the variability of a distribution from a great many differences in number between two neighboring

Table 19 Randomly distributed discs counted in divisions of different size.

|   | Observed S. D. given as a fraction of the S. D. expected for a Poisson distrib. with the same mean. |                              |                               |
|---|---|------------------------------|-------------------------------|
|   | Divisions 6.25 cm <sup>2</sup>  | Divisions 25 cm <sup>2</sup> | Divisions 100 cm <sup>2</sup> |
| Model Hl<br>Area 8100 cm <sup>2</sup><br>Disc no. 183 | 0.96  | 0.95                         | 0.84                          |
| Model Cc<br>Area 8100 cm <sup>2</sup><br>Disc no. 334 | 0.92  | 0.87                         | 0.86                          |
| Model Dd<br>Area 8100 cm <sup>2</sup><br>Disc no. 484 | 0.87  | 0.79                         | 0.70                          |
| Model Hh<br>Area 2025 cm <sup>2</sup><br>Disc no. 173 | 0.79  | 0.80                         | —                             |
| Model Aa<br>Area 2025 cm <sup>2</sup><br>Disc no. 227 | 0.75  | 0.65                         | —                             |
| Model Gg<br>Area 2025 cm <sup>2</sup><br>Disc no. 282 | 0.74  | 0.67                         | —                             |

divisions, according to the formula on page 8. Or a great many indices of dispersion are calculated from the counts in a few neighboring divisions a procedure developed by Fisher (26, 35-52). The reason for using these methods may e.g. be to avoid a systematic difference between different parts of a preparation. If we e.g. assess the variability from the differences between counts in divisions bordering upon each other the previously described blocking of neighbor divisions is expected to

Table 20. Comparing S. D. of division counts calculated in 4 different ways.

| Model | Div size | Orthodox method | Side neighbors | Diagonal neighbors | Distant neighbors |
|-------|----------|-----------------|----------------|--------------------|-------------------|
| Hh    | 6.25     | 0.579           | 0.592          | 0.564              | 0.559             |
| Aa    | 6.25     | 0.629           | 0.677          | 0.635              | 0.663             |
| Gg    | 6.25     | 0.692           | 0.718          | 0.668              | 0.705             |
| Ee    | 6.25     | 0.663           | 0.735          | 0.629              | 0.629             |
| Ff    | 4        | 0.64            | 0.662          | 0.612              | 0.662             |
| Tpkt  | 4        | 0.464           | 0.559          | 0.433              | 0.468             |

make itself felt in double dosage as to say. We are in such cases not comparing the occasional high count with a random partner but actually with a partner which will be on the low side. The S. D. will then become higher than if we had calculated it from a large number of independent counts from the same sample. And it will be higher than if we compared two neighboring partners which did *not* have a common border line.

In table 20 we have calculated the observed S. D. of individual division counts for the 6 disc models with the highest density of discs. For each model the observed S. D. was calculated in 4 different ways.

1 *Orthodox method* was from counts in multiple divisions according to the formula on page 27.

2 *Side neighbors* was from difference between counts in two quadratic divisions with one common side.

3 *Diagonal neighbors* was from the difference between counts in divisions with no common side but with one corner touching each other.

4 *Distant neighbors* was from the difference between counts in divisions separated by another division.

From the table it is seen that the S. D. calculated from orthodox method or from diagonal neighbors or from distant neighbors, differed very little. The S. D. cal-

culated from difference between side neighbors, however, tended to be somewhat higher than the S. D. calculated by the other methods, exactly as was expected.

What applied to two division counts making one pair will also apply to e.g. 4 division counts used for calculating an index of dispersion. If some of these divisions have a common border line, this will mean that an exceptionally large count in one division will be accompanied by a lower than usual count in one or more of the neighbor divisions. This will make the index of dispersion higher than if none of the divisions had a common border.

1) *Hypothesis for relationship between variable free area, and S. D. for counts in equal divisions.*

We shall now consider a random distribution of  $n$  discs in an area  $A$ , and also a random distribution of points in another area of the same size  $A$ . For the disc distribution the mean variable free area ( $\frac{A}{n-1}$  minus  $1.46 \times D$ ) will express the area over which each individual may vary. For the point distribution the mean free area ( $\frac{A}{n-1}$ ) will express the area over which each individual may vary.



Assume each of the two equal areas  $A$  divided into a number ( $n$ ) of equal divisions. Counting disc centers per division would enable us to find the S. D. for division counts in the first area  $A$ . Similarly we could count individuals per division in the second area  $A$  finding the S. D. for division counts of the randomly placed points. This latter S. D. would be close to  $\sqrt{\frac{n}{a}}$  as  $\frac{n}{a}$  would be the mean number per division.

We find it reasonable that there is a proportionality between S. D. for division count and the area over which each individual may vary for these two types of random distribution. (What we are speaking of as S. D. is in this connection nothing more than the square root of the variance, p. 17)

Our hypothesis is therefore

$$\frac{\text{S. D. division count} \times \text{discs}}{\text{S. D. division count} \times \text{points}} =$$

$$\frac{\text{mean variable free area} \times \text{discs}}{\text{mean free area} \times \text{points}}$$

Or written

$$\text{S. D. division count} \times \text{discs} =$$

$$n - 1 \frac{1}{4} \text{ minus } 1.46 D \sqrt{\frac{n}{a}}$$

Or written

$$\text{S. D. Disc distrib.} = \text{S. D. Poisson distrib.}$$

$$1 \text{ minus } \frac{1.46 D}{n - 1}$$

There is, however one thing this formula does not take into account. And that is the deviations caused by the disc centers in the border zone of each division. Our hypothesis therefore only applies to S. D. of counts in really large divisions where the effect of the border zones can be disregarded.

From preliminary tests on models it seemed that we might modify our formula for use with smaller divisions. When we multiplied Disc area ( $D$ ) in our formula

$$\text{with } \frac{\text{Division side minus Disc radius}}{\text{Division side}} \text{ the}$$

formula seemed to predict a S. D. which came close to the observed value. The

$$\text{factor } \frac{\text{Division side minus Disc radius}}{\text{Division side}} \text{ is}$$

easily calculated for the division sizes and disc size we are using. The disc radius is all the time 0.8 cm. Our smallest divisions have sides 2 cm, and the adapting factor thus will be  $\frac{2 - 0.8}{2} = 0.60$ . Divisions hav-

ing sides 2.5 cm will have adapting factor 0.68, those with sides 5 cm have factor 0.84. Divisions with sides 10 cm will have factor 0.92. As the sides approach unlimited size the adapting factor approaches 1. If, on the other hand, the sides approach the size of the disc radius, the adapting factor will approach zero, and the predicted S. D. of division counts will approach that of a Poisson distribution, regardless of disc density.

g) *Observed S. D. of division counts compared to our hypothetical value*

We do not think that these adapting factors which adapt our formula for counts in small divisions, necessarily are mathematically correct. If they however give a

Table 21 Model Hh. The distribution of disc centers in 324 divisions each 6.25 cm

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 |
| 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| 1 | 1 | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 |
| 0 | 0 | 1 | 3 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 |
| 1 | 0 | 1 | 0 | 1 | 2 | 0 | 0 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| 0 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 1 |
| 0 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 0 | 0 | 2 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 2 | 1 | 1 | 0 | 1 |
| 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 |
| 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 1 | 2 | 0 | 0 | 1 |
| 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| 0 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| 2 | 1 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |

fairly good approximation, we shall be satisfied. In that case we shall be able to predict the S. D. for randomly distributed discs counted in divisions of any given size.

The distribution of disc centers, which is the basis for the observed S. D., is in table 21 listed for one of the models. The observed and predicted S. D. for all 9 models, is compared in tables 22 and 23. When observed and expected S. D. is being compared we must always have in mind the number of individual division counts on which the S. D. is based. If the observed S. D. is based on counts in as few as 16 divisions, considerable deviation from the expected S. D. may be tolerated. If, on the other hand, the observed S. D. is based on counts in as many as 1296 divisions, only small deviations from the expected S. D. may be tolerated (For normal distributions e.g. the standard error of the S. D. is  $\frac{S.D.}{\sqrt{2n}}$  where  $n$  is the

number of observations on which the S. D. is based (97) )

Tables 22 and 23 show that where the observed S. D. was based on counts in a large number of divisions, it came quite close to the predicted value. When the observed S. D. was based on counts in relatively few divisions it was sometimes a little larger sometimes a little smaller than the expected value.

We had, however only 3 models with a reasonable large number of divisions sized 100 cm. And all these models (Ia, Cc, Dd) gave an observed S. D. lower than the expected value. Did this indicate that our hypothesis for the S. D. or our adapting factor were wrong or could it be due to chance?

In order to investigate this a little further we reexamined these 3 models. Model I' contained 183 disc centers distributed over 8100 cm<sup>2</sup>. During the plotting procedure 15 millimeter squares had been

Table 22 For randomly distributed discs Observed S. D. of individual division count compared  
 ■ value predicted by our hypothesis.

| Model                              | Observed and predicted S. D. as fraction of S. D. expected for<br>Poisson distribution with the same mean |               |               |                 |               |               |                               |               |               |                                  |
|------------------------------------|---|---------------|---------------|-----------------|---------------|---------------|-------------------------------|---------------|---------------|----------------------------------|
|                                    | Divisions 6.25 cm   |               |               | Divisions 25 cm |               |               | Divisions 100 cm <sup>2</sup> |               |               | Div.<br>co. sz.<br>Exp.<br>S. D. |
|                                    | Div.<br>no.   | Obs.<br>S. D. | Exp.<br>S. D. | Div.<br>no.     | Obs.<br>S. D. | Exp.<br>S. D. | Div.<br>no.                   | Obs.<br>S. D. | Exp.<br>S. D. |                                  |
| Model H<br>Area 8100<br>Discs 183  | 1,296   | 0.96          | 0.96          | 324             | 0.95          | 0.94          | 81                            | 0.84          | 0.94          | 0.93                             |
| Model Cc<br>Area 8100<br>Discs 334 | 1,296   | 0.92          | 0.92          | 324             | 0.87          | 0.90          | 81                            | 0.86          | 0.89          | 0.88                             |
| Model Dd<br>Area 8100<br>Discs 484 | 1,296   | 0.87          | 0.88          | 324             | 0.79          | 0.85          | 81                            | 0.70          | 0.84          | 0.83                             |
| Model Hh<br>Area 2025<br>Discs 178 | 324   | 0.79          | 0.83          | 81              | 0.80          | 0.79          | 16                            | 0.71<br>0.88  | 0.77          | 0.75                             |
| Model Aa<br>Area 20<br>Discs 72    | 324   | 0.73          | 0.78          | 81              | 0.63          | 0.73          | 16                            | 0.49<br>0.59  | 0.70          | 0.67                             |
| Model Gg<br>Area 2025<br>Discs 782 | 324   | 0.74          | 0.73          | 81              | 0.67          | 0.66          | 16                            | 0.53<br>0.72  | 0.63          | 0.59                             |
| Model Ee<br>Area 625<br>Discs 114  | 100   | 0.61          | 0.64          | 25              | 0.57          | 0.55          |                               |               |               | 0.47                             |

omitted, as they were located inside of previously drawn circles. The omitted millimeter squares had, however in each case been tagged. Model Cc contained 334 disc centers and 61 tagged squares and model Dd 484 disc centers and 140 tagged squares. If we counted disc centers plus tagged squares this total count

should follow the Poisson distribution. We then counted the total number of disc centers plus tagged squares in divisions 6.25 cm, 25 cm and 100 cm in size. Table 24 lists the observed S. D. of these counts compared with the expected square root of the mean, for the 3 models. It is seen that the observed values came very

Table 23 For randomly distributed discs. Observed S. D. of individual division count compared to value predicted by our hypothesis.

|                                   | Observed and predicted S. D., as fraction of S. D. expected for Poisson distrib. with the same mean |           |           |                 |           |           |                          |
|-----------------------------------|---|-----------|-----------|-----------------|-----------|-----------|--------------------------|
|                                   | Divisions 4 cm <sup>2</sup>   |           |           | Divisions 16 cm |           |           | Divisions unlimited size |
|                                   | Div. no.  | Obs. S.D. | Exp. S.D. | Div. no.        | Obs. S.D. | Exp. S.D. | Exp. S.D.                |
| Model P1<br>Area 256<br>Discs 54  | 64  | 0.70      | 0.64      | 16              | 0.68      | 0.51      | 0.59                     |
| Model Tpk<br>Area 256<br>Discs 62 | 64  | 0.47      | 0.58      | 16              | 0.37      | 0.44      | 0.50                     |

Table 24 Observed S. D. of randomly distributed individuals (disc centers plus tagged squares) compared with expected square root of the mean per division, for divisions of different size.

|                                    | Divisions 6.25 cm <sup>2</sup> |            | Divisions 25 cm |            | Divisions 100 cm |            |
|------------------------------------|--------------------------------|------------|-----------------|------------|------------------|------------|
|                                    | Obs. S. D.                     | Exp. S. D. | Obs. S. D.      | Exp. S. D. | Obs. S. D.       | Exp. S. D. |
| Model I<br>Area 8100<br>Indiv 198  | 0.39                           | 0.39       | 0.80            | 0.78       | 1.48             | 1.56       |
| Model Cc<br>Area 8100<br>Indiv 335 | 0.55                           | 0.55       | 1.06            | 1.10       | 2.08             | 2.21       |
| Model Dd<br>Area 8100<br>Indiv 624 | 0.69                           | 0.69       | 1.33            | 1.39       | 2.40             | 2.78       |

close to the expected values for counts in divisions 6.25 cm<sup>2</sup> and 25 cm but that the observed values were lower than expected for the counts in divisions 100 cm<sup>2</sup>. The deviations from the expected values

were respectively minus 5 per cent, minus 5 per cent and minus 15 per cent.

When we in table 22 had calculated the expected S. D. for disc centers counted in divisions sized 100 cm these expected

values had been given as a fraction of the square root of the mean ( $m$ ). This fraction was an expression of how much more uniform the disc distribution was expected to be. If the point random distribution now happened to be more uniform than expected, it is only reasonable that the disc distribution also be more regular than the expected value.

The deviations of the observed S.D. from the expected values when counting disc centers in divisions sized 100 cm<sup>2</sup> were therefore: all probability due to chance.

h) *Observed S.D. of counts in divisions 100 cm<sup>2</sup> compared in values expected by Turner & Eadie by Watanabe and by our hypothesis*

The observed S.D. of counts in various divisions have been found to agree well with values expected from our formula. Our formula included an adapting factor which allowed for the blocking effect of border zone discs, most marked with small divisions sizes.

The formulae of Turner & Eadie (85) and Watanabe (86-87) do not allow for this blocking effect. Their formulae were meant for counting erythrocytes: some

Table 3. Observed S.D. of randomly distributed discs compared to values predicted by Watanabe, Turner & Eadie, and our own formula, for individual divisions 100 cm<sup>2</sup> S.D. given as fraction of S.D. expected for Poisson distribution with the same mean.

|                                    | Divisions no. | Obs. S.D.    | Expected S.D. Watan. model | Expected S.D. T & E. model | Expected S.D. own model |
|------------------------------------|---------------|--------------|----------------------------|----------------------------|-------------------------|
| Model 11<br>Area 8100<br>Discs 183 | 81            | 0.84         | 0.97                       | 0.97                       | 0.94                    |
| Model 1C<br>Area 8100<br>Discs 334 | 81            | 0.86         | 0.95                       | 0.95                       | 0.89                    |
| Model Dd<br>Area 8100<br>Discs 484 | 81            | 0.70         | 0.93                       | 0.92                       | 0.81                    |
| Model Fth<br>Area 7025<br>Discs 15 | 16            | 0.71<br>0.68 | 0.90                       | 0.88                       | 0.77                    |
| Model Aa<br>Area 7025<br>Discs 27  | 16            | 0.43<br>0.39 | 0.87                       | 0.84                       | 0.70                    |
| Model Gg<br>Area 7025<br>Discs 22  | 16            | 0.53<br>0.49 | 0.83                       | 0.80                       | 0.63                    |

7-8  $\mu$  in diameter in divisions with sides 50  $\mu$ . This will be about the same relationship between diameter and division size as when we are counting discs with diameter 16  $\mu$ , in divisions with sides 10  $\mu$ . We have therefore in table 25 compared the observed S. D. for 6 of our counts in 100  $\mu$  divisions, with expected values from the formula of Turner & Eadie, as well as that of Watanabe, and our own formula. The S. D. is in each case given as a fraction of the S. D. for a Poisson distribution with the same mean. The S. D. expected from Turner & Eadie's as well as from Watanabe's formula, is all the time found to be considerably higher than the observed S. D. and also consistently higher than the value expected from our own formula. We do not think that Turner & Eadie's or Watanabe's formula can adequately predict the S. D. for discs counted in equal divisions. Our own formula, on the other hand, seems to predict the S. D. of such counts quite well.

#### 1) *Effect of variable disc size, random defects occasional overlapping*

Assume having a random distribution of discs which vary in size around a mean  $D$  rather than all being of the same size. Occasional places would then have a collection of only small discs, giving an increased density. Other places might happen to have only large discs, with a lowered density. The result of this variation in disc size, would be a somewhat less uniform distribution.

Assume having a random distribution of discs on a plane surface, with random defects superimposed. These defects could be assumed to be empty spaces of varying size. When disc centers are counted in equal divisions, such empty spaces will

result in a higher observed S. D., most marked with a high density of discs. The cells bordering on these empty spaces, keep their neighbors on all other sides. Their free area is therefore only rarely increased, and the observed mean free area will therefore remain practically unchanged. As the number ( $n$ ) of disc centers in the area ( $A$ ) has been lowered by these superimposed empty spaces, the mean free area expected from our formula

$\left(\frac{A}{n-1} \text{ minus } 1.46 \times D\right)$  will tend to be higher than the observed value. Random defects in a disc distribution would then be expected to result in a higher observed S. D. of individual division counts, and a lower mean variable free area.

Occasional overlapping of cells would likewise be expected to result in a higher observed S. D. of individual counts, and a lower observed mean variable free area, as compared to the values expected from our formulae.

### 3 Conclusions

1 The mean variable free area around randomly placed discs was defined. The hypothesis was set forth that this mean

variable free area was  $\frac{A}{n-1}$  minus  $1.46 \times D$  where  $A$  was total area,  $n$  was number of points, and  $1.46 \times D$  was the structures enclosed within mean free area.

This hypothesis was tested on 9 models with varying disc density. The observed mean variable free areas were found to be scattered around the hypothetical value, sometimes a little above, sometimes a little below. The difference between observed and hypothetical values was in no case significant.

2. When disc centers were counted in a number of equal divisions, the S. D. of an individual count was calculated in usual manner. This S. D. was expressed as a fraction of the expected S. D. for a Poisson distribution with the same mean. The percentage deviation from the S. D. of a Poisson distribution was found to increase with increased size of the divisions. The reason for this was thought to be a neighbor-blocking effect of the discs in the border zone, most marked with small division sizes.

3. A hypothesis was set forth for a relationship between variable free area and S. D. of count in equal divisions. The hypothesis was

$$\frac{\text{S. D. division count } n \text{ discs}}{\text{S. D. division count } n \text{ points}} =$$

$$\frac{\text{mean variable free area of } n \text{ discs}}{\text{mean free area of } n \text{ points}}.$$

The hypothesis was thought to apply only to the S. D. of counts in really large divisions, with insignificant blocking effect of border zone discs.

Adapting factors were introduced in order to allow for the blocking effect of border zone discs, thus adapting our hypothesis to counts in smaller divisions.

Our hypothesis was tested on all our 9 models of randomly placed discs. The observed values were found to be scattered around the hypothetical values, sometimes a little above sometimes a little below.

4. The formulae of Turner & Eadie and Watanabe, were found to give an expected S. D. systematically larger than the observed values.

5. Varying disc size, superimposed random defects and occasional overlapping were thought to result in a higher observed S. D. of individual division counts and lower observed mean variable free area, as compared to the values expected from our formula.

## C Erythrocytes in a blood smear

### 1 Diameter of erythrocytes

#### a Previous work

Accurate counts in haemocytometers have shown the distribution of erythrocytes to be somewhat more uniform than a Poisson distribution.<sup>5</sup> This is very likely due to the size of the erythrocytes. It is therefore not surprising that the mean diameter of the erythrocytes is an important factor in the theoretical model for distribution of erythrocytes in a counting chamber.<sup>30</sup> 43 85 86 87 These theoretical models will probably fit the smear situation no worse than the chamber situation. We shall therefore have to know the mean

erythrocyte diameter in order to compare the observed distribution with a theoretical model.

*Possible influence of smearing and drying*  
A great many different methods have been used for determining the erythrocyte diameter and the published normal value varies from one author to the other. From a review of literature it appears that opinions are divided as to the possible difference in size of erythrocytes in dry and wet preparations.

Some authors claim that the erythrocyte diameter is larger in a dry preparation, probably due to flattening during

spreading (20,57). Other authors claim that there is no difference between erythrocyte diameters in wet and dry preparations (7, 41, 91). The majority of authors, however, claim that the erythrocyte diameter is smaller in dry preparations than in wet ones (22, 72, 88, 89, 94).

When the erythrocyte diameter in wet and dry preparations is compared the optical conditions must be identical. This is because the erythrocyte diameter appears smaller with an oil immersion system than with a dry lens system (41, 43, 56, 65). The difference is 6—10 per cent. Larsen (57) in 1955 published an account of some interesting experiments, in which he tried to compare a wet and dry preparation with exactly the same optical system. Larsen measured the erythrocyte diameter on photographs. For 5 normal persons the mean erythrocyte diameter in a wet preparation was 6.6, 6.59, 7.21, 6.75 and 6.79  $\mu$ . The mean erythrocyte diameter in the dry preparation for the same five normal persons, was respectively 7.4, 7.17, 7.5, 7.18 and 7.52. In other words Larsen found a significantly larger diameter in the dry preparations.

On the other hand Houchin, Munn & Parnell (47) in 1958, as well as Westerman, Pierce & Jensen (89) in 1961 measured wet preparations with oil immersion system and found a normal mean erythrocyte diameter as large as respectively 8.28 and 8.56  $\mu$ .

Wells (88) in 1958 examined blood from different domestic animals in a wet as well as a dry preparation, using a dry lens system all the time. He found the mean erythrocyte diameter to be 0.5—1  $\mu$  smaller in the dry preparations.

The disagreement regarding size of erythrocyte diameter in dry and wet preparations thus does not appear to be quite settled. There is evidently room for further

investigations in this field. Such investigations, however, lie outside the limits of our present work. We shall accept the fact that the problem is not yet solved, that the erythrocyte diameter might either be somewhat larger in a wet preparation (22, 72, 88, 89, 94) or somewhat smaller (20, 57) or the same size as in a dry preparation (7, 41, 91).

A possible change in erythrocyte diameter during smearing or air drying will largely take place before the position of each cell has become fixed. For this reason the mean erythrocyte diameter in the dry preparation will probably be as appropriate to use in our models, or even more appropriate, than the diameter in the wet preparation.

*Possible influence of fixation and staining.* If the erythrocyte diameter changes during fixation or staining, such a change occurs after the erythrocyte position has become unchangeable. We should in such a case have to measure the diameter before fixing and staining our preparations. Several workers investigated this, concluding that fixation and staining does not influence the size of the erythrocytes (7, 59, 91).

*Accuracy of micrometer scales.* The degree of magnification of the photographs, or the projected image, is usually calculated by means of a micrometer scale engraved on a slide. Ponder (72) warns against accepting this scale at the maker's valuation, as it is comparatively rare for these micrometer scales to be individually calibrated.

#### b) On work

*Possible influence of fixation and staining.* The direction and degree of possible changes in size during smearing and drying did



Table 76. Blood smear PJS C, Area I Possible influence of fixation and staining upon erythrocyte diameter as measured on photographs. Measurement unit is  $\frac{1}{2}$  millimeter Photographed Oct. 26, with oil immersion.

| Cell | Diameter (average of longest and lateral) |         |               |         |                 |         |                   |         |
|------|---|---------|---------------|---------|-----------------|---------|-------------------|---------|
|      | Untreated covered                         |         | Fixed covered |         | Stained covered |         | Stained uncovered |         |
|      | Meas. 1                                   | Meas. 2 | Meas. 1       | Meas. 2 | Meas. 1         | Meas. 2 | Meas. 1           | Meas. 2 |
| A    | 22.5                                      | 22      | 22.5          | 22.5    | 22.5            | 22.5    | 21                | 20.5    |
| B    | 22.5                                      | 22.5    | 23            | 22.5    | 22.5            | 22.5    | 20.5              | 20.5    |
| C    | 22.5                                      | 22.5    | 23            | 22.5    | 22.5            | 22.5    | 20.5              | 20.5    |
| D    | 23  | 25      | 25            | 25      | 25              | 25      | 23                | 23      |
| E    | 21.5                                      | 21.5    | 22            | 22      | 22              | 22      | 20                | 20      |
| F    | 23.5                                      | 23.5    | 23            | 23      | 23.5            | 23      | 21.5              | 21      |
| G    | 23  | 23      | 23            | 23      | 23              | 23      | 21                | 21      |
| H    | 23.5                                      | 23      | 24            | 24      | 24              | 24      | 22.5              | 22      |
| I    | 22.5                                      | 22.5    | 22.5          | 22.5    | 22.5            | 22      | 20.5              | 20.5    |
| J    | 23.5                                      | 23.5    | 23.5          | 23.5    | 23.5            | 23.5    | 22                | 22      |
| K    | 26  | 26      | 26            | 26      | 26              | 26      | 24                | 24      |
| L    | 23.5                                      | 23.5    | 23.5          | 23.5    | 23.5            | 23.5    | 21.5              | 21.5    |
| M    | 22.5                                      | 22.5    | 22.5          | 22.5    | 22.5            | 22      | 20.5              | 20.5    |
| N    | 23.5                                      | 23      | 23.5          | 23.5    | 23.5            | 23.5    | 22                | 21.5    |
| O    | 21  | 21      | 21            | 21      | 21              | 21      | 19.5              | 19      |
| P    | 23.5                                      | 23.5    | 23.5          | 23.5    | 23.5            | 23.5    | 22.5              | 21.5    |
| Q    | 23.5                                      | 23.5    | 23.5          | 23.5    | 23.5            | 23.5    | 21.5              | 1.5     |
| R    | 22.5                                      | 22.5    | 22.5          | 22.5    | 22.5            | 22.5    | 20.5              | 20.5    |
| S    | 22  | 22      | 22            | 22      | 23              | 22.5    | 21                | 21      |
| T    | 2.5                                       | 2       | 23            | 23      | 23              | 22.5    | 21                | 21      |
| U    | 21.5                                      | 21.5    | 21.5          | 21.5    | 21              | 21      | 19.5              | 19.5    |
| V    | 23.5                                      | 23.5    | 23.5          | 23.5    | 23.5            | 23.5    | 22                | 22      |
| W    | 24  | 24      | 24            | 24      | 24.5            | 24      | 23                | 22      |
| X    | 23.5                                      | 23      | 23            | 23      | 23.5            | 23.5    | 22                | 21.5    |
| Y    | 23.5                                      | 23.5    | 23.5          | 23.5    | 23.5            | 23.5    | 22.5              | 22.5    |
| Z    | 24  | 4       | 23.5          | 24      | 24              | 24      | 22.5              | 22      |
| aa   | 23.5                                      | 23.5    | 23.5          | 23.5    | 23.5            | 23.5    | 21.5              | 1.5     |
| ab   | 1   | 23      | 22.5          | 23      | 22.5            | 22.5    | 21                | 20.5    |
| ac   | 23  | 23      | 23            | 23      | 23              | 23      | 1.5               | 1.5     |
| ad   | 23  | 25      | 25            | 25      | 25              | 24.5    | 23                | 23      |
| Bb   | 21.5                                      | 21.5    | 21.5          | 21.5    | 20.5            | 21      | 19.5              | 19.5    |
| Cc   | 23  | 23      | 23            | 23      | 23              | 23      | 21                | 21      |
| Dd   | 21  | 21      | 21            | 21      | 21.5            | 21      | 19.5              | 19.5    |
| Mean | 23.03                                     | 22.97   | 23.06         | 23.06   | 23.09           | 22.96   | 21.36             | 21.18   |

Table 27 Possible influence of fixation and staining upon erythrocyte diameter. Measurement unit is  $\frac{1}{2}$  millimeter. Photographed Oct. 26, with oil immersion.

| Smear                          | Area | No. of cells | Mean diameter |       |
|--------------------------------|------|--------------|---------------|-------|
|                                |      |              | Meas. I       | Meas. |
| PJS C,<br>untreated, covered   | I    | 33           | 23.05         | 22.97 |
|                                | II   | 28           | 22.11         | 22.11 |
| PJS C,<br>fixed, covered       | I    | 33           | 23.06         | 23.06 |
|                                | II   | 28           | 22.30         | 22.27 |
| PJS C,<br>stained, covered     | I    | 33           | 23.09         | 22.98 |
|                                | II   | 28           | 22.34         | 22.30 |
| PJS C,<br>stained, not covered | I    | 33           | 21.36         | 21.18 |
|                                | II   | 28           | 1.05          | 20.88 |
| PJS D<br>stained, not covered  | I    | 30           | 20.75         | 20.83 |
|                                | II   | 30           | 21.40         | 21.40 |

not concern us too much, as we in any case were inclined to use the diameter of the dry preparation.

A possible change in size during fixation or staining, on the other hand, would be of great importance. If such a change would be of any magnitude, we would have to measure the diameter before fixation and staining. Because of the great importance to our work, we repeated some previous investigations of the possible effect of fixation and staining.

Blood smears were made, and areas of faultless appearance were marked off after gross inspection and low power microscopy. An identification mark was made at a random point within these areas.

Photographs were made of the same field of view unstained and unfixed, after fixation, and after fixing and staining. Before fixation, immersion oil or serum will dissolve the erythrocyte of a smear. A thin cover slip was therefore in all cases

placed on top of the blood smears, protecting the erythrocytes from the oil. The thin cover slip constituted the roof of a chamber similar to that of Larsen (57). The only difference was that our thin cover slip rested on two strips of aluminum foil in stead of on two other cover slips, the working distance of our oil-immersion objective being shorter than that of Larsen's objective. Our cover slip was held tightly down on the strips of aluminum foil by strips of Scotch tape.

It was not practical to use the same cover slip and strips of aluminum foil for all photos of one particular field of view. The cover slips, however, were all from the same batch, and the strips of aluminum foil were all cut from the same sheet. The results are given in tables 26 and 27.

It appears that fixing and staining caused very little if any change in the erythrocyte diameter. In order to observe a possible influence of a change in optical

Table 28. S. D. of measurement of individual erythrocyte diameter assessed from different between measurement 1 and measurement 2. Measurement unit is  $\frac{1}{2}$  millimeter. Photographed Oct. 26., with oil immersion.

| Smear                       | Area | No. of cells | S. D. of measurement of individual diameter |
|-----------------------------|------|--------------|---|
| PJS C, untreated, covered   | I    | 33           | 0.14  |
|                             | II   | 28           | 0.29  |
| PJS C, fixed, covered       | I    | 33           | 0.12  |
|                             | II   | 28           | 0.5   |
| PJS C, stained, covered     | I    | 33           | 0.18  |
|                             | II   | 28           | 0.17  |
| PJS C, stained, not covered | I    | 33           | 0.25  |
|                             | II   | 28           | 0.42  |
| PJS D stained, not covered  | I    | 30           | 0.19  |
|                             | II   | 30           | 0.16  |

system we also photographed the same field after staining with no cover slip chamber the immersion oil lying directly on the blood smear Table 26 shows that the erythrocyte diameter was some 7.5 per cent smaller when the immersion oil was in direct contact with the blood smear.

Blind control measurements were carried out in all cases. For each photograph we calculated the S. D. of measurement of individual erythrocyte diameter by means of the difference between 1 and 2 measurement, table 28 Table 27 lists the mean diameter per photo for 1 and 2 measurement. The variability of enlargement between photographs is listed in table 29.

Table 29. Variability of enlargement between photographs processed on the same day. Measurement unit is  $\frac{1}{2}$  millimeter. Photographed Oct. 26. with oil immersion.

| Film | Picture number | Distance representing 70 $\mu$ |
|------|----------------|--------------------------------|
| 1    | 7              | 199.6                          |
| 1    | 12             | 199.7                          |
| 1    | 15             | 199.7                          |
| 1    | 18             | 199.6                          |
| 1    | 21             | 199.4                          |
| 1    | 25             | 199.8                          |
| 1    | 28             | 199.2                          |
| 1    | 32             | 199.7                          |
| 2    | 30             | 200.6                          |
|      | 33             | 200.3                          |
| 2    | 36             | 200.8                          |
|      |                | mean 199.85                    |

The difference between mean diameters in 1 and 2 measurement is in one case as large as 0.18 units (each unit  $\frac{1}{2}$  millimeter) in all other cases smaller. This small difference between 1 and 2 measurement, is thought to give more weight to our experimental findings. It makes it unlikely that unconscious bias has influenced our experimental findings to any significant degree.

*Our technique of photographing and measuring diameter.* Blood smears were prepared by spreading a small drop of blood on a slide by means of a thick, ground cover glass, held at about 30 degree angle. The smear was immediately air dried by waving in the air for about 15 seconds. Smears were stained within a couple of hours by May-Grünwald & Giemsa stain in usual manner. The smear used was always one which by gross inspection appeared to have a large area of faultless appearance. This area was then scrutinized

by low power microscopy magnification  $\times 80$ . We made certain that there were no large defects in the preparation, and no or practically no overlapping of erythrocytes. We marked off an area large enough to enclose at least one hundred different fields of view with magnification 800 times.

Different fields of view were picked randomly from the area marked off without looking into the microscope when picking each field for photography. No field was ever omitted afterwards.

*The camera* Zeiss photomicroscope.

*Source of light* 6 volt, 15 watt.

*Filter* F. A. L. yellow-green, 537 milli-micron.

*Substage condenser* Numerical aperture 0.9

|                  |               |          |
|------------------|---------------|----------|
| <i>Objective</i> | Oil immersion | 100/1.25 |
| Plane achromatic | High dry      | 40 0.63  |
|                  | Low dry       | 10 0.22  |

*Optecor* 1.25

*Projector* 3.2  $\times$

All parts of the camera were fixed, and the magnification on the film would therefore always be the same when the same lenses were used.

*Film* Kodak Panatomic —  $\times$

Copies were made on Kodak paper bromide, white, smooth, glossy. Usually hard, sometimes extra hard paper was used. During the copying the image on the film was enlarged. The degree of enlargement was exactly the same for each batch of photographs, but would vary slightly from one batch to the other around 3.5 times which always was the enlargement aimed at. The exact enlarge-

ment for each batch was ascertained by photographing a Zeiss micrometer scale once for every 5 pictures of erythrocytes. We always photographed the same part of the micrometer scale, as the ruling varied slightly from one part of the scale to the other. The part used was calibrated at the Department of Physics, University of Bergen.

No photographs were discarded. Only the erythrocytes in the center of each photograph were used. The reason for using only the central cells was that we also wanted to study the position of each cell in relation to the position of the closest neighbor.

We wanted to avoid the possibility of a systematic error in picking the erythrocytes to be measured. A window about  $5 \times 4$  cm was therefore made in the center of a washed roentgen film cut to the same size as the photographs. All erythrocytes appearing in this window were marked with letters A, B, C etc. for identification. The erythrocytes were then measured with a Faber's Castell ruler with a scale graded to 0.5 mm. We did not omit any marked erythrocyte, even if an occasional one was distorted, and many were not quite circular.

Measurements were made from the outer demarcation of the dark border line on one side to the outer demarcation on the other side as this was the only point which was sharply defined. This was in agreement with statements made by Larsen (58).

We can not, however, be sure that this outer demarcation of the dark border line observed with oil immersion system, represents the true border of the erythrocyte. That is, when two neighboring erythrocytes are just touching each other physically in the preparation, the outer demarcation of the dark border lines on a

photograph might not necessarily also touch each other. Perhaps the slightly larger erythrocyte size obtained with a dry lens system, would be more representative of the true size?

The longest erythrocyte diameter was measured and also the largest lateral diameter measured at 90 degrees angle to the longest cell diameter. The mean of these two figures were written down next to the letter identifying the measured cell. Blind control measurements were later carried out in all cases.

*Erythrocyte diameter in smears made from diluted and from undiluted blood.* During our investigation of the laws for the distribution

Table 30. Some blood values for the two persons PJS and JH

|                                       | British |      |
|---------------------------------------|---------|------|
|                                       | PJS     | JH   |
| Hemoglobin<br>(Gram per 100 ml blood) | 15.2    | 17.2 |
| Erythrocytes<br>Millions per mm blood | 5.11    | 5.26 |
| Hematocrit                            | 45      | 45   |

of erythrocytes in a smear we used blood from two healthy persons PJS and JH their blood values given in table 30. From each of these two persons we prepared a number of blood smears and chose one smear of faultless appearance made from undiluted blood and 3 smears made from different blood dilutions. The blood dilutions had been made by thoroughly mixing two drops of capillary blood with a few drops of serum, or plasma rendered uncoagulable by a small amount of powdered heparin.

By gross inspection and low power microscopy we marked off an area with no large defects and no or practically no overlapping of erythrocytes. The area was to be large enough to enclose at least one hundred consecutive fields of view with magnification 800 times.

From the area marked off 10 fields of view were picked for measurements. These fields were distributed at intervals, picked by means of the ruling on the microscope stage without looking into the microscope.

The number of erythrocytes whose diameter was measured ranged from 108 to 51 for the different areas. The results of the measurements are given in table 31. It is evident that the mean erythrocyte

Table 31. Observed mean erythrocyte diameter—two independent measurements. Measurement unit is  $\frac{1}{2}$  millimeter. Photographed Nov. 9 with oil immersion.

| Smear data   | No. of photos | Total no. of cell | Mean diameter |         |
|--------------|---------------|-------------------|---------------|---------|
|              |               |                   | Meas. 1       | Meas.   |
| PJS 1 undil. | 10            | 108               | 20.2500       | 20.1806 |
| JH II        | 10            | 81                | 18.0968       | 18.1049 |
| PJS IV       | 9             | 51                | 18.6961       | 18.7059 |
| PJS III      | 10            | 55                | 19.1818       | 19.1818 |
| JH I undil.  | 10            | 101               | 18.9807       | 19.0099 |
| JH III       | 10            | 97                | 18.4011       | 18.4021 |

Table 32 S. D. of measurement of individual erythrocyte diameter assessed from difference between measurement 1 and 2. Measurement unit is  $\frac{1}{2}$  millimeter. Photographed with oil immersion Nov. 9.

| Smear   | No. of photos. | Total no. of cells. | S. D. of measurement of individual diameter |
|---------|----------------|---------------------|---|
| PJS I   | 10             | 108                 | 0.1934                                      |
| JH II   | 10             | 81                  | 0.1620                                      |
| PJS IV  | 9              | 51                  | 0.1917                                      |
| PJS III | 10             | 55                  | 0.2132                                      |
| JH I    | 10             | 101                 | 0.2169                                      |
| JH III  | 10             | 97                  | 0.1759                                      |

diameter is smaller in the preparations made from diluted blood. On the photographs the border of the erythrocytes appeared slightly uneven in the preparations made from diluted blood. It seems as if there has occurred some shrinkage of the erythrocytes when 2 drops of blood have been thoroughly mixed with a few drops of serum or plasma on a slide or in a small glass tube. We have noticed this apparent shrinkage with interest, but have considered further investigation of the phenomenon to be outside the limits of the present work. If there occurs a shrinkage during dilution  $r$  is the diameter of the shrunken erythrocytes which will concern the distribution in a smear. The mean erythrocyte diameter observed in an area of a smear will therefore always be the diameter to be used in our mathematical formulae for erythrocyte distribution in that particular smear.

Blind control measurements were later carried out for each smear. The S. D. of measurement of individual diameter was calculated for each of the 6 smears, and is listed in table 32. Table 31 lists the mean

Table 33. Variability of enlargement between photographs processed on the same day. Measurement unit is  $\frac{1}{2}$  millimeter. Photographed with oil immersion Nov. 9.

| Film | Picture number | Distance representing 70 $\mu$ |
|------|----------------|--------------------------------|
| 1    | 1              | 194.35                         |
| 1    | 7              | 194.20                         |
| 1    | 13             | 194.35                         |
| 1    | 19             | 194.20                         |
| 1    | 25             | 194.30                         |
| 1    | 31             | 194.50                         |
| 1    | 37             | 195.10                         |
| 2    | 1              | 194.20                         |
| 2    | 7              | 194.00                         |
| 2    | 13             | 194.00                         |
| 2    | 19             | 194.15                         |
| 2    | 25             | 193.50                         |
| 2    | 31             | 193.50                         |
| 2    | 37             | 194.20                         |
| mean |                | 194.16786                      |

Table 34. Variability of enlargement between photographs processed on the same day. Measurement unit is  $\frac{1}{2}$  millimeter. Photographed with dry lens objective Nov. 9.

| Film | Picture number | Distance representing 70 $\mu$ |
|------|----------------|--------------------------------|
| 3    | 4              | 78.45                          |
| 3    | 7              | 78.3                           |
| 3    | 13             | 78.3                           |
| 3    | 19             | 78.3                           |
| 3    | 25             | 78.5                           |
| 3    | 31             | 78.5                           |
| mean |                | 78.425                         |

diameter of each smear for 1 and 2. measurement. The variability of enlargement between photographs is listed in tables 33 and 34. The difference between mean diameters in 1 and 2. measurement is in

one case as large as 0.07 units, in all other cases smaller. This small difference between 1 and 2 measurement is an indicator of the accuracy of our diameter measurements. It makes it unlikely that unconscious bias has influenced our measurements to any significant degree.

## 2 Mean variable free area around erythrocytes

### a) Previous work

We were not able to find any previous work concerning the distance from one disc center to the center of the closest neighbor for randomly distributed discs. We were likewise unable to find any work regarding the distance from the center of one erythrocyte to the center of the closest neighbor in a counting chamber or in a blood smear.

### b) Own work

*Mean variable free area on photographs of a blood smear.* Distance from the center of each erythrocyte to that of the closest neighbor was measured. The center of the erythrocytes was marked by piercing the center of a circle drawn on roentgen film, the circle carefully placed to match the erythrocyte border. From the center of each letter marked cell we measured the distance to the center of the closest neighbor by means of our Castell ruler with unit 1.2 millimeter. Tables 35-36 show the observed distance to the closest neighbor, the observed free area, and the observed mean free area, for each of the 11 smears photographed Nov. 9.

In tables 37 and 38 we have used the observed mean diameter for each particular smear to calculate the non-variable innermost Diameter<sub>1</sub> area. This innermost non-variable area is subtracted

from the observed mean free area to give the observed mean variable free area listed in tables 37 and 38. Observed mean variable free area was compared to the area expected from our formula for randomly distributed discs. In this formula the density of disc centers is needed, and this was obtained from the later count in 100 consecutive fields. These counts were always performed in an area of  $159.8333 \times 159.9$  units of each photograph (each unit was 1.2 millimeter). Each batch of 100 consecutive photographs was processed on a different day with a slightly different degree of enlargement. The number ( $n$ ) of erythrocytes counted, was therefore always adjusted to give the number ( $n/f$ ) corresponding to the magnification of the photographs used for the measurements (tables 39-43).

The two smears with the lowest density of cells were photographed with dry lens objective. With the low density of cells in these two preparations, the influence of a slight change in diameter would be small. In stead of measuring the diameter in these low density preparations, we used the average diameter observed in the two other smears made of diluted blood from the same person. The observed mean free area of the dry lens photographs, was adjusted to the value corresponding to oil immersion magnification (table 43). In table 46 the observed mean variable free area is compared to the value expected from our formula for randomly placed

discs ( $\frac{A}{n-f} \text{ minus } 1.46 \cdot D$ ) see page 39. The observed mean variable free area is found to be higher than the expected value in 3 cases, lower in 5 cases. The deviations on the low side of the expected value, in addition to being more frequent, also were of a greater magnitude than the deviations on the high side. This fits well

Table 35. Distance to closest neighbor for random erythrocytes in 6 different blood smears. Photographed Nov 9 with oil immersion. Measurement unit is  $\frac{1}{2}$  millimeter

| Distance           | PJS I |                    | JH I |                    | JH III |                    | JH II |                  | PJS III |                    | PJS IV |                    |
|--------------------|-------|--------------------|------|--------------------|--------|--------------------|-------|------------------|---------|--------------------|--------|--------------------|
|                    | No.   | Free area<br>x no. | No.  | Free area<br>x no. | No.    | Free area<br>x no. | No.   | Free area<br>no. | No.     | Free area<br>x no. | No.    | Free area<br>x no. |
| 10                 |       |                    |      |                    |        |                    |       |                  |         |                    | 2      | 628                |
| 11                 |       |                    |      |                    |        |                    |       |                  |         |                    |        |                    |
| 12                 |       |                    |      |                    | 1      | 432                |       |                  |         |                    | 3      | 1,357              |
| 13                 |       |                    |      |                    |        |                    |       |                  | 4       | 2,124              |        |                    |
| 14                 |       |                    |      |                    |        |                    |       |                  |         |                    |        |                    |
| 15                 |       |                    |      |                    |        |                    |       |                  | 2       | 1,414              | 1      | 707                |
| 16                 |       |                    |      |                    | 2      | 1,608              |       |                  |         |                    |        |                    |
| 17                 |       |                    |      |                    | 4      | 3,631              |       |                  |         |                    | 1      | 908                |
| 18                 |       |                    | 4    | 4,068              | 4      | 4,068              |       |                  |         |                    | 2      | 2,034              |
| 19                 | 15    | 17,010             | 12   | 13,608             | 15     | 17,010             | 2     | 2,268            | 6       | 6,804              | 1      | 1,134              |
| 20                 | 16    | 20,112             | 7    | 33,939             | 14     | 17,398             | 10    | 12,570           | 1       | 1,237              | 2      | 2,514              |
| 21                 | 28    | 38,808             | 23   | 31,878             | 21     | 29,108             | 16    | 22,176           | 1       | 1,386              | 10     | 13,860             |
| 22                 | 25    | 38,000             | 27   | 41,040             | 23     | 34,960             | 16    | 24,320           | 16      | 24,320             | 3      | 4,560              |
| 23                 | 18    | 29,916             | 5    | 8,310              | 2      | 3,324              | 16    | 26,592           | 4       | 6,648              | 3      | 8,310              |
| 24                 | 5     | 9,045              | 1    | 1,809              | 3      | 9,045              | 4     | 7,236            | 3       | 5,427              | 4      | 7,236              |
| 25                 | 1     | 1,963              | 1    | 1,963              | 4      | 7,852              | 5     | 9,815            | 1       | 1,963              | 4      | 7,852              |
| 26                 |       |                    | 1    | 1,123              | 2      | 4,246              | 2     | 4,246            | 3       | 6,369              | 1      | 2,123              |
| 27                 |       |                    |      |                    |        |                    | 3     | 6,870            | 1       | 2,290              | 3      | 6,870              |
| 28                 |       |                    |      |                    |        |                    | 1     | 2,462            |         |                    |        |                    |
| 29                 |       |                    |      |                    |        |                    | 1     | 2,642            |         |                    | 3      | 7,926              |
| 30                 |       |                    |      |                    |        |                    | 2     | 5,654            | 2       | 5,654              | 2      | 5,654              |
| 31                 |       |                    |      |                    |        |                    | 1     | 3,018            | 1       | 3,018              |        |                    |
| 32                 |       |                    |      |                    |        |                    | 1     | 3,217            | 3       | 16,085             |        |                    |
| 33                 |       |                    |      |                    |        |                    |       |                  | 1       | 5,421              | 1      | 5,421              |
| 34                 |       |                    |      |                    |        |                    | 1     | 3,631            |         |                    |        |                    |
| 35                 |       |                    |      |                    |        |                    |       |                  | 1       | 3,849              |        |                    |
| 36                 |       |                    |      |                    |        |                    |       |                  |         |                    | 1      | 4,070              |
| 37                 |       |                    |      |                    |        |                    |       |                  | 2       | 8,600              |        |                    |
| 38                 |       |                    |      |                    |        |                    |       |                  | 1       | 4,336              |        |                    |
| 40                 |       |                    |      |                    |        |                    |       |                  |         |                    | 1      | 5,025              |
| 49                 |       |                    |      |                    |        |                    |       |                  |         |                    | 1      | 7,543              |
| Total no.          | 108   |                    | 101  |                    | 97     |                    | 81    |                  | 55      |                    | 51     |                    |
| Total area         |       | 154,854            |      | 136,758            |        | 132,900            |       | 136,717          |         | 105,163            |        | 93,732             |
| Obs mean free area |       | 1,433.83           |      | 1,373.64           |        | 1,370.10           |       | 1,687.86         |         | 1,912.09           |        | 1,837.88           |



Table 41. Number ( $\times f$ ) of erythrocytes in 400 divisions each (80 units). If the enlargement of photographs makes 831 79174 (prototyp  $\mu$ ) represent (80 units)<sup>2</sup> on photographs. This is the enlargement of the photographs of these 6 smears taken Nov. 9 and used for measuring diameter and mean free area. Photographed with oil immersion.

| Smear date of photographs | (Prototyp $\mu$ ) represented by (80 units) | 831 791 4 divided by thin (prototyp $\mu$ ) <sup>2</sup> ( $f$ ) | Observed erythrocyte number in 400 $\times$ (80 units) <sup>2</sup> ( $\kappa$ ) | $\kappa / f$ |
|---------------------------|---|--|--|--------------|
| PJS I March 2             | 807.03090                                   | 1.03710  | 3 627  | 5 761.56     |
| JH II June 22             | 746.91797                                   | 1 11363  | 2,453  | 2 731.73     |
| PJS IV May 10             | 813.03994                                   | 0.98665  | 1,851  | 1,828.26     |
| PJS III Apr. 13           | 794.55883                                   | 1.04685  | 2 183  | 285.27       |
| JH I June 5               | 776.01031                                   | 1.07184  | 3,365  | 3,606.74     |
| JH III June 29            | 808.92254                                   | 1.02827  | 3 435  | 3,532.11     |

Table 42. Different portions of our Zeiss micrometer measured on photographs with the same enlargement. Measurements unit is  $\frac{1}{2}$  millimeter intervals 0-7 named prototyp  $0\mu$  and other portions measured with this prototyp. Photographed with dry lens objective Dec. 1

| Picture number | Micrometer portion | Distance representing 15 micrometer intervals |                       |          | Micrometer portion measured with 0-7 as prototyp |
|----------------|--------------------|---|-----------------------|----------|--|
|                |                    | Meas. 1                                       | Meas.                 | Mean     |  |
| 1              | 0-7 15<br>7        | 79.03 $\times$ 15<br>7                        | 79.0 $\times$ 15<br>7 | 169.2857 | 150 $\mu$  |
| 8              | 10-7 15<br>7       | 79 $\times$ 15<br>7                           | 79 $\times$ 15<br>7   | 169.2837 | 150 $\mu$  |
| 3              | 30-45              | 170.2   | 170.1                 | 170.2    | 150.81 $\mu$                                     |
| 7              | 83-98              | 167.0   | 167.0                 | 167.0    | 147.97 $\mu$                                     |

Table 43. Area of smear in (prototyp  $\mu$ ) represented by (80 units) on photographs, for each of 2 different batches of photographs. Photographed with dry lens objective. Unit  $\frac{1}{2}$  millimeter

| Micro-meter portion | Prototyp $\mu$ in these 15 intervals | Smear date of photogr | Distance representing these 15 micrometer intervals |         |       | Prototyp $\mu$ represented by 80 units on photos. | (Prototyp $\mu$ ) represented by (80 units) on photos. |
|---------------------|--------------------------------------|-----------------------|---|---------|-------|---|--|
|                     |                                      |                       | Meas. 1   | Meas. 2 | Mean  |   |  |
| 30-45               | 150.81                               | JH IV Aug. 24         | 176.95  | 176.95  | 177.0 | 68.1627   | 4 646.15367  |
| 83-98               | 147.97                               | PJS II July 4         | 170.4   | 170.45  | 170.4 | 69.4695   | 4,826.01143  |

Table 44. Number ( $\times f$ ) of erythrocytes in 400 divisions each (80 units)\* If the enlargement of photographs make 5098.788274 (prototyp  $\mu$ ) represent (80 units) on photographs. This is the enlargement of the photographs of these 2 smears taken Nov 9 and used for measuring mean free area. Dry lens objective.

| Smear date of photography | (Prototyp $\mu$ ) represented by (80 units)* | 5098.788274 divided by this (prototyp $\mu$ ) ( $f$ ) | Observed erythrocyte number in 400 $\times$ (80 units) ( $\times$ ) | $\times f$ |
|---------------------------|--|---|---|------------|
| JH IV Aug 24              | 4,646.15367                                  | 1.0974  | 6,206   | 6,810.46   |
| PJS II July 9             | 4,826.01143                                  | 1.0563  | 2,127   | 2,247.18   |

Table 43. Expected mean variable free area calculated from formula  $\frac{A}{n-1}$  minus  $1.46 \times D$ . The area of 100 photos with dry lens objective for smears JH IV and PJS II is multiplied with 6.15542 in order to give corresponding area for oil immersion enlargement. As diameter in JH IV we used the average of JH II and JH III and as diameter in PJS II we used the average of PJS II and IV. Unit is  $\frac{1}{2}$  millimeter. Enlargement corresponding to photographs of Nov 9.

| Smear   | Area of 100 photos (A) | Total cells minus 1 ( $n-1$ ) | $\frac{A}{n-1}$ | $1.46 \times$ (area of one cell) ( $1.46 \times D$ ) | Expected mean var free area |
|---------|------------------------|-------------------------------|-----------------|--|-----------------------------|
| PJS I   | 2,333.734              | 3,760.56                      | 679.615         | 470.208  | 209.407                     |
| JH I    | 2,333.734              | 3,603.74                      | 708.796         | 415.087  | 293.709                     |
| JH III  | 2,333.734              | 3,531.11                      | 723.776         | 388.507  | 335.469                     |
| JH II   | 2,333.734              | 2,750.73                      | 933.916         | 375.612  | 560.304                     |
| PJS III | 2,333.734              | 2,284.27                      | 1,118.841       | 421.909  | 696.932                     |
| PJS IV  | 2,333.734              | 1,827.26                      | 1,398.670       | 400.813  | 997.857                     |
| JH IV   | 13,731.616             | 6,809.46                      | 2,310.258       | 381.960  | 1,928.298                   |
| PJS II  | 13,731.616             | 2,246.18                      | 7,003.720       | 411.361  | 6,592.359                   |

brated to be 99.85 and 100.00 millimeters respectively in each of calibrations. The difference between each 10 units portion of the ruler was hardly any greater than the error of the method of calibration.

From the calibration we may conclude that our Castell ruler was almost exactly the size it was manufactured to be. The Zeiss micrometer as a whole was also close to the size it was manufactured to be. But the portion we had chosen as our

"prototyp portion, was 71.8  $\mu$  and not the 70  $\mu$  it was manufactured to be.

All of our measurements of diameter as well as measurements of distance to closest neighbor were done with the same calibrated Faber Castell ruler with unit

millimeter. All other portions of the micrometer used for measurements, were rephotographed and compared to the prototyp portion. As far as comparing observed mean variable free area and ob-

Table 46 Observed mean variable free area compared to value expected from our formula

$$\frac{A}{n-1} \text{ minus } 1.46 \quad D$$

| Smear   | Expected mean var. free area | No. of areas measured | Observed mean var. free area |
|---------|------------------------------|-----------------------|------------------------------|
| PJS I   | 201.407                      | 108                   | 145.58                       |
| JII I   | 295.709                      | 101                   | 211.88                       |
| JII III | 535.463                      | 97                    | 306.4                        |
| JII II  | 560.304                      | 81                    | 408.78                       |
| PJS III | 696.932                      | 55                    | 751.16                       |
| PJS IV  | 997.817                      | 51                    | 739.75                       |
| JII IV  | 1928.298                     | 158                   | 1687.46                      |
| PJS II  | 6542.359                     | 64                    | 6753.85                      |

served S D of counts to values expected by our hypothesis all distances refer to our uncalibrated prototyp portion. Comparison of our erythrocyte diameters to values from the literature however demands reference to the calibrated prototyp portion. If we thus measured an erythrocyte diameter of  $7 \mu$  by reference to our prototyp portion, the calibrated value would be  $7.18$ .

When we made the photographs to be used for measuring the diameter and distance to the closest neighbor every 6th picture was of our micrometer the same prototyp portion of it each time. The variation from one photo to the other is shown to be quite small tables 29-33 and 34.

### 3 S D for counts in equal divisions

#### a) *Poisson count*

The basis for assessing the distribution error in a counting chamber is the variability in number of erythrocytes in different divisions. Observed distribution errors in counting chambers have been published a great many times.

Knowledge of the distribution error in a blood smear is also of considerable practical importance when an indirect reticulocyte count is performed with a Millar ocular disc (15-66-76) or a similar instrument (92).

Previous work in this field is scarce or lacking. Schneiderman and Brecher (76) made the theoretical assumption that the total erythrocytes in their reticulocyte preparations followed the Poisson distribution, but did not publish any actual observations regarding the distribution of erythrocytes in a smear.

#### b) *Own work*

*Technique of counting and method of calculating S D.* An expression of the distribution of erythrocytes in smears was obtained by counting cells in each of a great many divisions. The smears and the areas within each smear were the same as used for the measurements of diameter and distance previously described.

In these 8 smears cells were counted in 10 divisions (fig. 12) within each of 100 consecutive fields of view using microscope with oil immersion system.

As a check on possible unconscious bias in counting the same general area of the smear but not necessarily the same fields of view were photographed. Pictures were made of 100 consecutive fields, and erythrocytes counted in each of 4 divisions of each photo. Two independent counts were made showing little if any unconscious bias.

The results of microscope counts were compared with those of photographic counts. The 8 microscope counts were made with oil immersion system. Six smears were photographed with oil immersion system 2 with dry lens system. A photograph taken with oil immersion system for technical reasons covered only

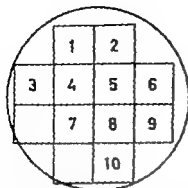


Fig 12. The relative position of the 10 divisions of a microscopical field of view

about half the area surveyed in one field during a microscope count. This was kept in mind when our procedure was planned.

In the blood smear there could very well be a systematic difference, the density of cells e.g. being greater in one side than in the other. Each field of view was therefore regarded as a separate sample, for the microscope counts. The distribution within each field of view was assessed from the number of cells in the various divisions. In order to be comparable in area to the microscope count each two consecutive

photos made with oil immersion system were pooled to one sample.

Another detail which was to be remembered was that divisions within the same sample should not have a common border. A common border might cause the distribution to appear less uniform than it is (p. 43).

During our microscope counts, a glass with an engraved ruling divided each field into 10 equal divisions. The glass plate was taken from a telemeter and was mounted into a frame which could be screwed into the lower end of our ocular. The total magnification was 800 times. Cells lying on left or upper border were included but not those lying on right or lower border. No single field of view was omitted. All counts were made by the author using 4–6 hours on each smear. The 10 divisions were numbered from 1–10. Fig 12 shows the location of the divisions. Their distance from the center of the microscope field varied somewhat. The total count in each division for the 8 microscope counts, is given in table 47. The difference between the total count for each of the 10 divisions is seen to be small.

Table 47 (A) Microscope Total number of cells in each of the 10 divisions for the 8 microscope counts. I PJS II 200 fields of view were counted, in the other smears 100 fields.

| Smear   | Divisions |       |       |       |       |       |       |       |       |       | Total  |
|---------|-----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|
|         | 1         | 2     | 3     | 4     | 5     | 6     | 7     | 8     | 9     | 10    |        |
| PJS I   | 1,334     | 1,345 | 1,335 | 1,311 | 1,293 | 1,319 | 1,343 | 1,354 | 1,329 | 1,335 | 13,296 |
| PJS II  | 272       | 277   | 282   | 266   | 288   | 280   | 278   | 274   | 284   | 274   | 2,775  |
| PJS III | 832       | 793   | 787   | 796   | 781   | 739   | 763   | 783   | 753   | 784   | 7,813  |
| PJS IV  | 633       | 658   | 699   | 664   | 708   | 688   | 684   | 678   | 690   | 673   | 6,773  |
| JH I    | 1,333     | 1,338 | 1,34  | 1,362 | 1,332 | 1,309 | 1,339 | 1,321 | 1,297 | 1,339 | 13,312 |
| JH II   | 1,013     | 1,013 | 996   | 968   | 983   | 984   | 993   | 1,017 | 993   | 1,021 | 9,983  |
| JH III  | 1,290     | 1,303 | 1,232 | 1,228 | 1,256 | 1,266 | 1,268 | 1,276 | 1,209 | 1,443 | 12,571 |
| JH IV   | 411       | 416   | 399   | 448   | 428   | 432   | 387   | 425   | 402   | 387   | 4,135  |
| Total   | 7,118     | 7,143 | 7,072 | 7,043 | 7,069 | 7,017 | 7,039 | 7,128 | 6,957 | 7,054 | 70,660 |

Table 48. (Phot.) Erythrocytes counted in 4 divisions on each of 100 consecutive photographs of each blood smear

| Smear date           | Count 1            |                |             | Count 2<br>Grand total |
|----------------------|--------------------|----------------|-------------|------------------------|
|                      | Total for each div |                | Grand total |                        |
| PJS I<br>March 2.    | 875<br>909         | 910<br>933     | 3,627       | 3,631                  |
| JII II<br>June 22.   | 622<br>620         | 640<br>571     | 2,453       | 2,455                  |
| PJS IV<br>May 10.    | 442<br>487         | 444<br>450     | 1,835       | 1,851                  |
| PJS III<br>April 13. | 566<br>539         | 535<br>545     | 183         | 1,182                  |
| JII I<br>June 5.     | 815<br>838         | 882<br>830     | 3,365       | 3,362                  |
| JII III<br>June 29   | 870<br>844         | 854<br>867     | 3,435       | 3,443                  |
| JII IV<br>August 24  | 1,532<br>1,566     | 1,593<br>1,515 | 6,206       | 6,214                  |
| PJS II<br>July 2     | 533<br>531         | 548<br>515     | 127         | 2,127                  |
|                      | 6,25<br>6,334      | 6,434<br>6,226 | 25,449      | 25,263                 |

No total division count differed by more than 109 from the mean total division count. A systematic error producing an excessively high or low count in some of the divisions, was thus unlikely. Only the counts in the divisions 1 5 7 and 10 were used for assessing the distribution of the erythrocytes within each field of view. One of our reasons for using only these 4 divisions was that none of them had a common border. A common border could have caused the distribution to appear less regular than it actually was.

When photographing the fields to be counted 100 consecutive fields were taken, no single field of view being omitted. On a washed roentgen film fine lines engraved 4 quadratic divisions each with sides almost exactly 80 units measured with our Faber-Castell ruler with unit 1 millimeter. The left and upper border of the engraved divisions were made to coincide with the left and upper border of the photos. The cells in each division were then counted with our previous counting technique. All counts were done by the author using 4—5 hours on each batch of 100 photos. The total count in each division for the 8 photographic counts is given in table 48. It is seen that there is a certain excess of cells in the right upper division and somewhat fewer cells in the right lower division. Most of this difference is caused by smears JII IV and PJS II the smears with the lowest density of cells. The difference might therefore possibly be due to coincidence although we suspect that at least part of the difference might be due to some systematic error.

Each two photos made with oil immersion system were pooled to one sample. From each such sample we used two sets of divisions. One set consisted of left upper and right lower division of each of the two photos. The other set was the left lower and right upper division of each photo. It will be noticed that the area covered, and the positioning of each division were somewhat similar to those for the microscope count.

Each photo taken with dry lens objective was considered a separate sample. The erythrocyte distribution within each sample was assessed from the difference between left lower — right upper and the difference between left upper — right lower division.

For the microscope counts and for

Table 49 (PJS I Phot.) Observed index of dispersion ( $X^2 = \frac{S(\bar{x})}{\bar{x}}$ ) for each of 100 photos, arranged according to numerical value.

|       |       |       |       |       |       |       |       |
|-------|-------|-------|-------|-------|-------|-------|-------|
| 0.000 | 0.070 | 0.077 | 0.086 | 0.091 | 0.091 | 0.095 | 1.103 |
| 0.105 | 0.118 | 0.118 | 0.118 | 0.118 | 0.200 | 0.200 | 0.200 |
| 0.200 | 0.222 | 0.222 | 0.222 | 0.222 | 0.222 | 0.282 | 0.282 |
| 0.282 | 0.282 | 0.282 | 0.297 | 0.297 | 0.297 | 0.297 | 0.297 |
| 0.297 | 0.314 | 0.316 | 0.316 | 0.333 | 0.333 | 0.333 | 0.333 |
| 0.333 | 0.463 | 0.487 | 0.487 | 0.487 | 0.487 | 0.487 | 0.500 |
| 0.514 | 0.514 | 0.528 | 0.528 | 0.543 | 0.543 | 0.600 | 0.600 |
| 0.600 | 0.667 | 0.667 | 0.667 | 0.730 | 0.730 | 0.818 | 0.889 |
| 0.889 | 0.946 | 0.946 | 0.947 | 0.947 | 1.000 | 1.000 | 1.059 |
| 1.061 | 1.061 | 1.103 | 1.294 | 1.294 | 1.368 | 1.368 | 1.368 |
| 1.368 | 1.578 | 1.578 | 1.513 | 1.529 | 1.545 | 1.556 | 1.595 |
| 1.619 | 1.645 | 1.759 | 2.000 | 2.030 | 2.444 | 2.459 | 2.471 |
| 2.862 | 3.414 | 3.960 | 4.226 |       |       |       |       |

Total  $10.150 + 11.094 + 11.841 + 12.699 + 8.621 + 9.262 + 9.495 + 9.699 = 82.861$

Observed total  $X^2 = 82.861$   $S() = 100$   $3 = 300$

Expected total  $X^2$  Poisson  $= \frac{2S() - 1}{2} = 299.5$

Obs. total  $X^2 = \frac{82.861}{299.5} = 0.27666$

Obs. S. D. indiv div count  $= \sqrt{0.27666} = 0.526$

counts on photos taken with oil immersion the S. D. of individual division count was calculated in two different ways. 1) In one way the S. D. was calculated from the difference in count between corresponding divisions within each sample e.g. both left upper divisions both right upper divisions etc.

For microscope counts we used the difference between division 1 and 7 and between 5 and 10 of each field of view fig 11 2) Whenever feasible, the S. D. of individual division count was also calculated by an "index of dispersion method" This method was somewhat similar to the one described by Fisher Thornton & MacKenzie (35) and called "test of agree-

ment with Poisson series of a number of small samples" (34) As Lancaster (35) has pointed out, a prerequisite for using this way of testing, is that each sample consists of at least 4 divisions, and that the mean per division is at least 5

This way of testing was therefore only applied to 6 microscope counts, and 4 counts on photos. When the index of dispersion method was used, an index of dispersion was calculated for each field of view of a microscope count, and for each of the two sets per photographic sample. First the mean was calculated, the deviation of each individual from this mean was squared and then the sum of the four squares was divided by the mean to give

Table 50 (Jill Phot.) Observed index of dispersion ( $V^2 = \frac{S(\bar{x})}{\bar{x}}$ ) for each of 100 photos, arranged according to numerical value

|       |       |       |       |       |       |       |       |
|-------|-------|-------|-------|-------|-------|-------|-------|
| 0.006 | 0.091 | 0.091 | 0.091 | 0.091 | 0.097 | 0.103 | 0.103 |
| 0.103 | 0.10  | 0.105 | 0.105 | 0.118 | 0.118 | 0.200 | 0.200 |
| 0.200 | 0.222 | 0.222 | 0.222 | 0.222 | 0.250 | 0.250 | 0.250 |
| 0.250 | 0.250 | 0.250 | 0.250 | 0.297 | 0.314 | 0.314 | 0.314 |
| 0.314 | 0.314 | 0.316 | 0.353 | 0.35  | 0.355 | 0.355 | 0.355 |
| 0.355 | 0.379 | 0.379 | 0.500 | 0.514 | 0.514 | 0.514 | 0.526 |
| 0.526 | 0.576 | 0.576 | 0.576 | 0.588 | 0.588 | 0.600 | 0.600 |
| 0.600 | 0.667 | 0.667 | 0.697 | 0.730 | 0.750 | 0.750 | 0.771 |
| 0.771 | 0.771 | 0.771 | 0.857 | 0.871 | 0.889 | 0.889 | 1.000 |
| 1.000 | 1.000 | 1.000 | 1.048 | 1.061 | 1.166 | 1.200 | 1.207 |
| 1.207 | 1.229 | 1.250 | 1.291 | 1.291 | 1.296 | 1.378 | 1.387 |
| 1.387 | 1.400 | 1.500 | 1.513 | 1.903 | 2.185 | 2.371 | 2.680 |
| 3.000 | 3.194 | 3.414 | 3.485 |       |       |       |       |

Total 9.851 + 10.198 + 10.541 + 11.018 + 8.044 + 8.518 + 8.924 + 9.593 = 76.487

Observed total  $V^2 \sim 76.487$   $S(\bar{x}) \sim 100$   $\bar{x} \sim 300$

Expected total  $V^2$  Poisson  $2S(\bar{x}) - 1 \sim 299.5$

Obs. tot  $V^2$   $\frac{76.487}{299.5} \sim 0.25538$

Obs. S. D. indiv. div. count  $\sqrt{0.25538} \sim 0.505$   
 Exp. S. D. indiv. div. count Poisson

what Fisher calls an index of dispersion. For each smear we thus calculated 100 indices of dispersion as listed in tables 49—52 according to numerical value.

Fisher *et al.* have shown that for true samples of a Poisson series the indices of dispersion will be distributed in a known manner (34—35). This manner of distribution is given by a Goodness of Fit table when it is entered with  $n$  one less than the number of divisions. In our cases  $n$  thus was 3.

From the formula for calculating Fisher index of dispersion it is evident that this index will vary proportionately with the variance provided the mean and the number of cases is kept constant. If the

variance of individual division count would be  $0.25 \times$  (the variance of a Poisson distribution) the deviations from the mean when calculating an index of dispersion would also be  $0.25 \times$  (the deviations of a Poisson distribution). And the S. D. of individual division count would be  $0.5 \times$  (the S. D. of a Poisson distribution).

Our 100 independent values of  $x$  (chi square) were added to give the observed total  $x$ . For a Poisson distribution the expected total  $x$  is itself distributed in the manner shown in the Table of  $x^2$  provided we take for  $n$  the number  $S(n)$  calculated by adding the several values of  $n$  for the separate experiments (34). In our case

Table 51 (JH II Phot.) Observed index of dispersion ( $X^2 = \frac{S(x-\bar{x})^2}{\bar{x}}$ ) for each of 100 photos, arranged according to numerical value.

|       |       |       |       |       |       |       |       |
|-------|-------|-------|-------|-------|-------|-------|-------|
| 0.091 | 0.097 | 0.103 | 0.170 | 0.153 | 0.143 | 0.154 | 0.176 |
| 0.182 | 0.286 | 0.286 | 0.333 | 0.333 | 0.333 | 0.379 | 0.400 |
| 0.407 | 0.440 | 0.440 | 0.440 | 0.440 | 0.440 | 0.462 | 0.478 |
| 0.524 | 0.524 | 0.524 | 0.524 | 0.545 | 0.647 | 0.667 | 0.667 |
| 0.704 | 0.704 | 0.760 | 0.769 | 0.769 | 0.769 | 0.826 | 0.857 |
| 0.837 | 0.857 | 0.857 | 0.905 | 0.905 | 0.909 | 0.909 | 0.931 |
| 0.931 | 1.000 | 1.000 | 1.111 | 1.174 | 1.174 | 1.174 | 1.200 |
| 1.200 | 1.200 | 1.200 | 1.207 | 1.207 | 1.207 | 1.385 | 1.385 |
| 1.385 | 1.400 | 1.429 | 1.467 | 1.483 | 1.600 | 1.600 | 1.636 |
| 1.667 | 1.667 | 1.842 | 1.842 | 1.870 | 2.000 | 2.000 | 2.000 |
| 2.000 | 2.263 | 2.364 | 2.364 | 2.500 | 2.586 | 2.680 | 2.777 |
| 2.778 | 2.800 | 2.913 | 2.923 | 2.923 | 3.074 | 3.105 | 3.320 |
| 3.320 | 3.966 | 4.333 | 5.240 |       |       |       |       |

Total 16.046 + 17.204 + 18.051 + 19.245 + 14.782 + 14.882 + 15.341 + 15.827 = 130.878

Observed total  $X^2 = 130.878$   $S(\bar{x}) = 100$   $S = 300$

Expected total  $X^2$  Poisson =  $\frac{2S(\bar{x}) - 1}{2} = 299.5$

Obs. total  $X^2$  =  $\frac{130.878}{299.5} = 0.43699$

Obs. S. D. indiv div count =  $\sqrt{0.43699} = 0.661$   
Exp. S. D. indiv div count Poisson

with 100 photos of 4 divisions each, the corresponding value of  $s$  was  $100 \cdot 3 = 300$

A good approximation of expected  $x^2$  is given by assuming that  $(\frac{1}{2}x - \frac{1}{2}n - 1)$  is normally distributed about zero with unit standard deviation (34). As our value of  $s$  was 300  $\frac{1}{2}x^2$  was expected to vary around  $\frac{1}{2}600 - 1$  and the observed total  $x^2$  was expected to vary around 299.5 provided the erythrocytes follow the Poisson distribution. Tables 49-52 show the observed total  $x^2$  to be considerably smaller than corresponding to a Poisson distribution. In these tables the total  $x^2$  is also given as a fraction of the total  $x^2$  expected for a Poisson distribution with the

same mean and the same number of divisions. The square root of this fraction, gives the S. D. of individual division count, expressed as a fraction of the expected S. D. for a Poisson distribution with the same mean.

*Attempts to check on unconscious bias* It is possible that the person counting cells in the four divisions of each sample might unconsciously cluster the counts closer to each other than they should be or opposite might spread them too much apart. Blind control counts were therefore done on all photographs.

Table 48 shows the difference between first and second count on the 11 sets of



Table 52. (JH III Phot.) Observed index of dispersion ( $V^2 = \frac{S(x - \bar{x})^2}{\bar{x}}$ ) for each of 100 photos, arranged according to numerical value.

|       |       |       |       |       |       |       |       |
|-------|-------|-------|-------|-------|-------|-------|-------|
| 0.000 | 0.000 | 0.001 | 0.001 | 0.006 | 0.009 | 0.118 | 0.133 |
| 0.154 | 0.222 | 0.223 | 0.222 | 0.250 | 0.268 | 0.282 | 0.286 |
| 0.286 | 0.297 | 0.314 | 0.314 | 0.316 | 0.333 | 0.333 | 0.333 |
| 0.333 | 0.333 | 0.400 | 0.407 | 0.440 | 0.444 | 0.444 | 0.476 |
| 0.514 | 0.514 | 0.526 | 0.526 | 0.526 | 0.526 | 0.543 | 0.543 |
| 0.545 | 0.576 | 0.576 | 0.600 | 0.613 | 0.613 | 0.667 | 0.667 |
| 0.667 | 0.667 | 0.730 | 0.730 | 0.30  | 0.771 | 0.818 | 0.897 |
| 0.931 | 0.931 | 0.94  | 1.000 | 1.000 | 1.000 | 1.059 | 1.059 |
| 1.059 | 1.065 | 1.065 | 1.111 | 1.129 | 1.200 | 1.207 | 1.2.6 |
| 1.230 | 1.294 | 1.294 | 1.294 | 1.368 | 1.429 | 1.457 | 1.457 |
| 1.457 | 1.457 | 1.467 | 1.529 | 1.545 | 1.545 | 1.5.6 | 1.686 |
| 1.811 | 1.811 | 1.903 | 1.914 | 2.000 | 2.178 | 2.178 | 2.211 |
| 2.439 | 3.30  | 3.710 | 4.433 |       |       |       |       |

Total  $11.486 + 12.430 + 13.251 + 14.203 + 10.023 + 10.348 + 10.612 + 10.908 = 93.356$

Observed total  $V^2 = 93.356$   $S(1) = 100$   $S = 300$

Expected total  $V^2$  Poisson  $= \frac{2S(1) - 1}{S} = 299.5$

Obs. total  $V^2 = 93.356$

Exp.  $V^2$  Poisson  $= 299.5 = 0.31171$

Obs. S. D. indiv. d. count  $= \sqrt{0.31171} = 0.558$

Exp. S. D. indiv. d. count Poisson  $= \sqrt{0.31171} = 0.558$

Table 53. Phot. S. II of individual division count due to counting technician, assessed from difference between count 1 and count 2 and expressed as fraction of one cell.

| Smear   | No. of Divisions | Mean no. of cells per div | S. D. of individual division count due to technician |
|---------|------------------|---------------------------|--|
| PJS I   | 400              | 9.0725                    | 0.1937   |
| PJS II  | 400              | 5.3175                    | 0.1225   |
| PJS III | 400              | 5.4563                    | 0.1541   |
| PJS IV  | 400              | 4.6300                    | 0.0866   |
| JH I    | 400              | 8.4088                    | 0.1541   |
| JH II   | 400              | 6.1350                    | 0.0866   |
| JH III  | 400              | 8.3973                    | 0.1582   |
| JH IV   | 400              | 15.5230                   | 0.1732   |

photographs and table 53 gives the S. D. of individual division count due to counting technician. The small number of differences between 1st and 2nd count was thought to indicate that the element of unconscious bias was rather insignificant.

Observed S. D. of division counts compared to hypothetical value for ideal discs. The observed S. D. of division counts for blood smears was compared to the hypothetical value for randomly distributed ideal discs with the same density. The formula used for calculating the hypothetical S. D. was

$$\frac{1}{n-1} \text{ minus } 1.46 \times D \quad (\text{adapt. fact.})$$

$$\frac{1}{n-1}$$

Table 54 (Phot) S. D. of individual division count on photographs expected from our hypothesis for randomly placed discs, expressed as fraction of the S. D. expected for a Poisson distribution with the same mean. All areas as (prototyp  $\mu$ )

| Smear   | Area of<br>400 div<br>(A) | No. of<br>rbc<br>( ) | Mean<br>diam. | Area of<br>one rbc<br>(D) | Adapt<br>fact.<br>(fact.) | $\frac{A}{n-1}$ minus<br>$\frac{1}{46} \times \text{fact.} \times D$ | $\frac{A}{n-1}$ | Hypo-<br>thetical<br>S. D. |
|---------|---------------------------|----------------------|---------------|---------------------------|---------------------------|--|-----------------|----------------------------|
| PJS I   | 520,812                   | 3,627                | 7.3004        | 41.8587                   | 0.8711                    | 35.2396  | 88.4755         | 0.998                      |
| JH II   | 298,767                   | 2,433                | 6.5.48        | 33.4370                   | 0.8806                    | 78.8562  | 118.462         | 0.647                      |
| PJS IV  | 337,216                   | 1,803                | 6.7402        | 35.6810                   | 0.8839                    | 136.0338   | 182.0821        | 0.747                      |
| PJS III | 317,224                   | 2,183                | 6.9153        | 37.5600                   | 0.8773                    | 97.5466  | 143.6372        | 0.670                      |
| JH I    | 310,416                   | 3,363                | 6.8426        | 36.7734                   | 0.8772                    | 45.1802  | 92.2739         | 0.490                      |
| JH III  | 323,569                   | 3,435                | 6.6342        | 34.5677                   | 0.8834                    | 49.6397  | 94.2231         | 0.527                      |
| JH IV   | 1,838,480                 | 6,206                | 6.5795        | 34.0009                   | 0.9517                    | 252.2657   | 299.5100        | 0.842                      |
| PJS II  | 1,930,404                 | 2,127                | 6.6278        | 36.6144                   | 0.9509                    | 357.1663   | 907.9981        | 0.944                      |

Table 55 (Microscope) S. D. of individual division count in microscope, expected from our hypothesis for randomly placed discs, expressed as fraction of the S. D. expected for a Poisson distribution with the same mean. All areas as (prototyp  $\mu$ )

| Smear   | Area of<br>all div<br>(A) | No. of<br>rbc<br>( ) | Area of<br>one cell<br>(D) | Adapt.<br>factor<br>(fact.) | $\frac{A}{n-1}$ minus<br>$\frac{1}{46} \times \text{fact.} \times D$ | $\frac{A}{n-1}$ | Hypo-<br>thetical<br>S. D. |
|---------|---------------------------|----------------------|----------------------------|-----------------------------|--|-----------------|----------------------------|
| PJS I   | 462,400                   | 3,303                | 41.8587                    | 0.8926                      | 32.6625  | 87.2124         | 0.5745                     |
| JH II   | 462,400                   | 4,012                | 33.4370                    | 0.9040                      | 71.1316  | 113.2830        | 0.6172                     |
| PJS IV  | 462,400                   | 2,698                | 35.6810                    | 0.9009                      | 124.5181   | 171.4498        | 0.7063                     |
| PJS III | 462,400                   | 3,162                | 37.5600                    | 0.8983                      | 97.0223  | 146.2828        | 0.6633                     |
| JH I    | 462,400                   | 5,343                | 36.7734                    | 0.8994                      | 38.2713  | 86.5593         | 0.4421                     |
| JH III  | 462,400                   | 5,057                | 34.5677                    | 0.9024                      | 45.9126  | 91.4557         | 0.5020                     |
| JH IV   | 462,400                   | 1,613                | 34.0009                    | 0.9032                      | 242.0126   | 286.8486        | 0.8457                     |
| PJS II  | 924,800                   | 1,112                | 36.6144                    | 0.8996                      | 784.3133   | 832.4032        | 0.9422                     |

expressed as a fraction of the S. D. expected for a Poisson distribution, with the same mean. All distances were expressed in prototyp  $\mu$ . The sides of each division during our microscope counts, were measured to be  $3\frac{1}{2}$  prototyp  $\mu$ .

The calculation of the hypothetical S. D. for the photographic counts is shown in table 54, that for the microscope counts in table 55.

In table 56 the observed S. D. of division counts on photographs is compared to the hypothetical value for ideal discs. The observed S. D. is seen to be fairly close to the hypothetical value, but the observed S. D. is always the larger value.

In table 57 the observed S. D. of division counts in microscope is compared to the hypothetical value for ideal discs. Again the observed S. D. is seen to fall

Table 56. (Phot.) Observed S. D. of individual divisions count on photographs compared to S. D. expected from our hypothesis for randomly placed discs. S. D. is in each case expressed as fraction of the S. D. expected for a Poisson distribution with the same mean.

| Smear   | Hypothetical S.D. | Observed S. D.              |                            |
|---------|-------------------|-----------------------------|----------------------------|
|         |                   | Multiple differences method | Index of dispersion method |
| PJS I   | 0.398             | 0.508                       | 0.526                      |
| JH II   | 0.647             | 0.642                       | 0.661                      |
| PJS IV  | 0.747             | 0.816                       |                            |
| PJS III | 0.670             | 0.780                       |                            |
| JH I    | 0.490             | 0.405                       | 0.405                      |
| JH III  | 0.57              | 0.558                       | 0.558                      |
| JH IV   | 0.81              | 1.033                       |                            |
| PJS II  | 0.944             | 1.032                       |                            |

Table 57 (Microscope) Observed S. D. of individual divisions count in microscope compared to S. D. expected from our hypothesis for randomly placed discs. The S. D. is in each case expressed as fraction of the S. D. expected for a Poisson distribution with the same mean.

| Smear   | Hypothetical S.D. | Observed S. D.              |                            |
|---------|-------------------|-----------------------------|----------------------------|
|         |                   | Multiple differences method | Index of dispersion method |
| PJS I   | 0.3745            |                             | 0.570                      |
| JH II   | 0.6172            |                             | 0.691                      |
| PJS IV  | 0.7263            |                             | 0.63                       |
| PJS III | 0.6633            |                             | 0.786                      |
| JH I    | 0.4421            |                             | 0.541                      |
| JH III  | 0.5020            |                             | 0.571                      |
| JH IV   | 0.8457            | 0.919                       |                            |
| PJS II  | 0.9122            | 0.985                       |                            |

reasonably close to the hypothetical value and again the observed S. D. is the larger value.

The deviations of the observed S. D. on the high side of the hypothetical value for ideal discs fit well with a random

distribution of discs having varying disc size or random defects superimposed, see page 49.

#### 4 Discussion

In chapter II C 1 "Diameter of erythrocytes" several technical difficulties were reviewed or investigated.

The question of a possible change in size during smearing and drying is not yet quite settled. If there is a change in size the results will differ according to whether the wet or the dry diameter is used in our formula. Provided there is a change in size during smearing and drying one might think that a certain part of this possible change occurs before the position of each erythrocyte has become fixed. In such a case a value somewhere between the wet and the dry diameter will be the most appropriate to use in our formula.

If the size of the erythrocytes changes during fixation and staining this would be very important and we should have to use the diameter observed before fixation and staining. Previous investigations as well as our own, showed practically no change during fixation and staining.

It has previously been pointed out, notably by Ponder (72) that micrometers should not be taken at the manufacturer's value. Our own investigations showed that the distance between 7 intervals varied considerably in different parts of the micrometer. All measurements and counts were therefore compared to the same "prototype portion" of the micrometer.

We made one smear from undiluted, and three from diluted blood, from each of two normal persons. The observed diameter was in all cases significantly lower in the smears made from diluted blood and the photographs suggest a certain amount of shrinkage. This shrinkage prob-

ably occurred while a few drops of blood were mixed with a few drops of serum or plasma on a slide or in a small tube. The diameter used in our models and for formulae, always was the one observed in that particular preparation, whether the erythrocytes were shrunken or not. This observation of shrinkage during dilution and mixing is worth remembering when we e.g. evaluate the results of a comparison of wet and dry preparations (57). If the wet preparation is made by diluting blood in serum or plasma, shrinkage might possibly make the erythrocytes in the wet preparation appear smaller than they are in undiluted blood.

At various stages of the diameter measurement three different decisions or choices of procedure had to be made, each of which might influence the value of the observed diameter.

1 The diameter could be measured in a wet or a dry preparation. We chose to measure the diameter in a dry preparation. The diameter thus measured might be too low or too high, depending upon the direction of a possible change in diameter during smearing and drying.

2 The photographs could be made with oil immersion, or with dry lens system. We chose to use oil immersion, for one thing because the diameter on the photographs would be larger and therefore easier to measure. If a dry lens system had been used a larger erythrocyte diameter would have been obtained.

3 The point of the erythrocyte from which to measure, also had to be decided upon. We chose to measure the diameter from the outer edge of the dark borderline on one side of the erythrocyte to the outer edge on the other side. For one thing this point was the only one sharply defined. Larsen (58) also advised us to use this measuring point. If we had measured

e.g. from the inner edge of the dark borderline on one side to the outer edge on the other side, a smaller erythrocyte diameter would have been measured. Obviously what we would be most interested to know is just when two erythrocytes are barely in physical contact with each other. Is it when the outer edges of the dark borderlines also are just in contact? And will this be true for photographs made with oil immersion system? These are very difficult questions, which we are not capable of solving presently.

The observed mean variable free area as well as the observed S. D. of individual division counts, were in all cases compared with hypothetical values for randomly placed ideal discs with the same diameter and the same density. The observed mean variable free area tended to be slightly lower than the hypothetical value for ideal discs and the observed S. D. of individual division counts tended to be somewhat larger than the hypothetical value.

If we e.g. think that the erythrocyte diameter used has been too small, we may calculate the hypothetical mean variable free area and the hypothetical S. D. using a larger diameter. The hypothetical mean variable free area is calculated from the formula

$$\frac{4}{\pi - 1} \text{ minus } 1.46 \cdot D \quad \text{A larger diameter will imply a larger disc area } D$$

and thus a smaller hypothetical mean variable free area. The hypothetical S. D. is calculated from the formula S. D. Poisson  $(1 \text{ minus } \frac{1.46 \cdot D}{\frac{4}{\pi - 1}})$  and a larger disc diameter will therefore imply a smaller hypothetical S. D. If we would calculate the hypothetical values using a larger erythrocyte diameter the observed mean variable free area might therefore come closer but the observed

S. D. would deviate still further from the hypothetical value.

If we e.g. think that the erythrocyte diameter used has been too large we may calculate the hypothetical mean variable free area and the hypothetical S. D. using a smaller diameter. Our observed mean variable free area would then deviate still further but the observed S. D. might come closer to the hypothetical value.

Blind control measurements were made of all diameters, and of all counts on photographs. The difference between 1st and 2nd measurement or count was quite small table 32 and table 33. We thought that if there had been a considerable amount of unconscious bias the difference between 1st and 2nd measurement or count would probably have been larger. This is because we think that it is almost impossible for a rather large unconscious bias to remain fairly constant during two measurements or counts.

The distance from one erythrocyte center to that of the closest neighbor was measured before the hypothetical mean variable free area was calculated. The measurement conditions thus probably favored unbiased observations, and the omission of the blind control was probably not of any consequences.

Gross inspection of the blood smears selected for use in our investigation, always showed a large area of faultless appearance. This area was scrutinized by low power microscopy and it was made certain that there were no large defects in the preparations, and no or practically no overlapping of erythrocytes. The erythrocyte distribution encountered in our 8 blood smears was therefore not the distribution of just any odd blood smear. The erythrocytes in the blood smears investigated were probably as uniformly distributed as is possible.

We have noticed that blood samples

from different persons differ in their ability to produce a good smear. Some blood samples produce smears with obviously less uniform erythrocyte distribution than others, sometimes with a tendency towards a net like arrangement of the erythrocytes. We do not know the cause of such a net like appearance.

## 5 Conclusions

1 Reasons are given for measuring the erythrocyte diameter in dried preparations, with oil immersion system. Own investigations verify the fact that fixation and staining causes only insignificant change in diameter of erythrocytes.

2 The observed mean variable free area around erythrocytes was compared with the area expected according to our hypothesis for randomly distributed ideal discs. The observed mean variable free area tended to be slightly smaller than the hypothetical area. This was thought to fit well with the fact that the erythrocytes are *not* ideal discs with perfectly random distribution and no overlapping. Occasional overlapping and randomly placed defects in a smear will tend to make the observed mean variable free area somewhat smaller than our hypothetical value for ideal discs.

3 The observed S. D. of individual division count was calculated in different ways and was compared with the S. D. expected according to our hypothesis for randomly distributed ideal discs. The observed S. D. tended to be somewhat larger than the hypothetical value. This was thought to fit very well with the fact that the erythrocytes are *not* ideal discs with perfectly random distribution and no overlapping. Occasional overlapping and randomly placed defects in a smear will tend to make the observed S. D. of individual division count somewhat larger than our hypothetical value for ideal discs.

### III Two sets of randomly placed individuals

#### A Two sets of randomly placed points

##### 1 Previous work.

If the probability of an event occurring is  $p$  and the probability of it not occurring is  $q = (1 - p)$  the frequencies of occurrence in samples of  $n$  trials will be given by the expansion of the binomial  $(p + q)^n$ . The binomial distribution was found by J. Bernoulli (1654—1705) and is sometimes named after him the Bernoulli distribution (29). A great number of different events have been found to follow the binomial distribution more or less closely. Dice throwing where 12 dice were thrown a great many times, 5 or 6 points being reckoned a success (34). Drawing 7 balls from a bag with equal number of black and white balls,  $p$  being 0.5  $q$  0.5 (97). Sex ratio in German families with 8 children (34). Proportion of barley ears infected with goutfly ascertained by examining samples of 100 ears (34). Proportion dying in samples of 100 patients with pneumonia (46). Proportion of monocytes among 100 leukocytes in cow blood (29). Many more examples could be given.

In all these examples the number of successes ( $p \times n$ ) out of a fixed number ( $n$ ) of trials have been counted. The condition absolutely necessary is that for each trial the chance of success is to be  $p$ , and the chance of failure is to be  $q$ .

##### 2 Own example of two sets of randomly placed individuals

As long as the chances of success and of failure in a binomial distribution are randomly mixed the trials may be uniformly spaced like e.g. telephone poles, or irregularly spaced like dice throwing with smoking and drinking pauses interspaced. Of course, the trials might also be randomly spaced.

When dealing with the Poisson distribution (p. 23) it was stated that a characteristic feature for that distribution was that the chance of an individual falling into one particular division was constant, the division being e.g. of time or of area. At times we may have two independent events, each following the Poisson distribution. We may e.g. have the occurrences of male births per hour of the day from 3 A. M.—9 A. M. following the Poisson distribution fairly closely and the occurrences of female births per hour of the day as another Poisson distribution, independent of the first one (disregarding multiple births). The sum of occurrences of two independent Poisson distributions will also follow the Poisson distribution (34) and the occurrences of births per hour irrespective of sex, would thus also follow the Poisson distribution. As a matter of fact, observations have shown the occurrences

of births per hour from 3 A. M.—9 P. M. to follow the Poisson distribution fairly closely (46). If we have a mean number ( $m_1$ ) of male births per hour and a mean number ( $m_2$ ) of female births, the chance of one birth being a male is constantly  $p = \left( \frac{m_1}{m_1 + m_2} \right)$ . The chance of it being

a female is constantly  $q = \left( 1 - \frac{m_1}{m_1 + m_2} \right)$ .

If random samples of e.g. a consecutive births are taken the frequencies of male births will therefore follow the binomial distribution. Or more generally,

When each of two independent events is following the Poisson distribution, the sum of the two events will also follow the Poisson distribution. And the frequency of one particular event in a random sample of the two events will follow the binomial distribution.

The following example was chosen from the death records of the Department of Health of the City of Bergen to illustrate the relationship.

In Bergen as probably in most other cities in the Northern hemisphere there is a low total death rate in the late summer and autumn and a winter maximum (39). We examined the death records of Bergen for the 3 years 1958—1960. The total number of deaths for these three years varied very little being respectively 1156, 1186 and 1166. During these three years the death rate was found to remain practically constant during January, February and March. The number of deaths per day for these three months were then computed for the three years 1958—1960. It gave a total of 931 deaths distributed on 271 days, a mean of 3.4355 per day. Table 58 lists the observed frequency of days with respectively 0—10 deaths

Table 58. Observed frequency of days with 0—10 deaths per day compared with frequency expected for a Poisson distribution.

| Total number of deaths per day | Observed frequency | Expected frequency | Measure of divergence       |
|--------------------------------|--------------------|--------------------|-----------------------------|
| 0                              | 7                  | 8.71               | 0.3357                      |
| 1                              | 33                 | 30.00              | 0.9000                      |
|                                | 48                 | 31.31              | 0.239                       |
| 3                              | 67                 | 58.98              | 1.0905                      |
| 4                              | 44                 | 50.67              | 0.8780                      |
| 5                              | 35                 | 34.81              | 0.0010                      |
| 6                              | 19                 | 19.93              | 0.0434                      |
| 7                              | 10                 | 9.78               | 0.0049                      |
| 8                              | 7                  | 4.50               |                             |
| 9                              | 0                  | 1.60               | 0.2523                      |
| 10                             | 1                  | 0.53               |                             |
| 11 and more                    | 0                  | 0.35               |                             |
|                                | 71                 | 271.09             | Chi square<br>3.1450<br>= 7 |

Measure of divergence is  $\frac{x^2}{m}$  where  $m$  is the expected value and  $x$  the difference between the expected and observed values.  $h$  degrees of freedom.

per day. The expected frequencies for a Poisson distribution are also given in the table as well as the values of the measure of divergence. The aggregate of these values is the Chi square, which is 3.145 corresponding to a  $P$  of between 0.9 and 0.8. There is thus no reason to suspect that the number of deaths per day for the period examined does not follow a Poisson distribution.

Among the total 931 deaths 92 persons were born on the 5th, 15th or 25th of a month. In table 49 are listed the observed frequencies of days with respectively 0, 1, 2 and 3 deaths amongst these five days born. From the observed mean 0.3395

Table 59 Observed frequency of days with 0, 1, 2, 3 deaths per day of "fivedayborn" compared with frequency expected for a Poisson distribution.

| Number of deaths per day among persons born 5th, 15th or 25th of a month. | Observed frequency | Expected frequency | Measure of divergence   |
|---|--------------------|--------------------|-------------------------|
| 0   | 196                | 192.985            | 0.0471                  |
| 1   | 60                 | 65.515             | 0.4642                  |
|   | 13                 | 11.120             |                         |
| 3   | 2                  | 1.259              |                         |
| 4   | 0                  | 0.107              | 0.4685                  |
| 5   | 0                  | 0.075              |                         |
| 6 and more  | 0                  | 0.012              |                         |
|   | 271                | 271.071            | Chi sq<br>0.9798<br>= 1 |

death per day amongst the "fivedayborn" the expected frequencies for a Poisson distribution were calculated, and the results are listed in table 59. The Chi square value corresponds to a  $P$  of between 0.5 and 0.3. As was to be expected also the deaths amongst the "fivedayborn" were thus found to be distributed in the Poisson series.

The total 931 deaths were then divided into 93 groups each of 10 consecutive deaths, the last death being discarded. Table 60 lists the observed frequencies of groups with respectively 0, 1, 2, 3, 4, 5 "five dayborn". By means of formula

$$1 = \frac{10!}{0!10!} p^{10} + \frac{10!}{1!9!} p^9 q + \frac{10!}{2!8!} p^8 q^2 + \frac{10!}{3!7!} p^7 q^3 + \frac{10!}{4!6!} p^6 q^4 + \frac{10!}{5!5!} p^5 q^5$$

the expected frequencies for a binomial or Bernoulli distribution were calculated from an observed  $p$  of 0.098925 (25). Table 60 lists the expected frequencies next to the observed values. The Chi square corresponds to a  $P$  of between 0.9 and 0.8, and there is thus no reason to suspect that the ratio "fivedayborn" to total deaths does not follow the binomial distribution.

### 3. Own work on models.

*Theoretically calculated mean free area.* Assume two sets (set 1 and set 2) of points randomly placed in a certain area  $A$ , the number of points in each set being respectively  $n_1$  and  $n_2$ , and each set being independent of the other. When points are randomly distributed on a plane surface, the number of points in areas similar in size will necessarily follow the Poisson distribution. Each of our two sets of points will therefore conform to the Poisson distribution.

When a number is the sum of several

Table 60. Observed frequency of 0, 1, 2, 3, 4, 5 "fivedayborn" in groups of 10 consecutive deaths, compared to frequency expected for binomial distribution.

| Number of persons born 5th, 15th or 25th in one group. | Observed frequency | Expected frequency | Measure of divergence  |
|--|--------------------|--------------------|------------------------|
| 0  | 33                 | 32.815             | 0.0010                 |
| 1  | 37                 | 36.0275            | 0.0763                 |
| 2  | 16                 | 17.8000            | 0.1780                 |
| 3  | 6                  | 5.2110             |                        |
| 4  | 0                  | 1.0310             |                        |
| 5  | 1                  | 0.1319             | 0.0650                 |
| 6  | 0                  | 0.0121             |                        |
| 7  | 0                  | 0.0008             |                        |
| 8  | 0                  | 0.0000             |                        |
|  | 93                 | 92.9993            | Chi sq.<br>0.2703<br>= |



Table 61 Model Ff. Investigation of one set of discs randomly mixed among another set of discs.

|   | Right half            | Left half             |
|---|-----------------------|-----------------------|
| Area of each half sheet ( $A$ )   | 1 012.5 cm            | 1 012.5 cm            |
| True number of discs per half sheet ( $n$ )                                   | 33.5                  | 33.5                  |
| Area of each disc ( $D$ )   | 2.01 cm               | .01 cm                |
| Hypothetical mean variable free area $\frac{A}{n-1}$<br>minus $1.46 \times D$ | 28.22 cm              | 28.22 cm              |
| Observed mean variable free area  | 26.61 cm <sup>2</sup> | 24.57 cm <sup>2</sup> |
| Observed S. D. of individual var free area                                    | 24.50 cm <sup>2</sup> | 20.57 cm              |
| Observed number of discs  | 36                    | 31                    |

Table 62 Model Aa. Investigation of one set of discs randomly mixed among another set of discs.

|   | Right half | Left half             |
|---|------------|-----------------------|
| Area of each half sheet ( $A$ )   | 1 012.5 cm | 1 012.5 cm            |
| True number of discs per half sheet ( $n$ )                                   | 44         | 44                    |
| Area of each disc ( $D$ )   | 2.01 cm    | 2.01 cm               |
| Hypothetical mean variable free area $\frac{A}{n-1}$<br>minus $1.46 \times D$ | 20.61 cm   | 20.61 cm              |
| Observed mean variable free area  | 15.67 cm   | 13.19 cm <sup>2</sup> |
| Observed S. D. of individual var free area                                    | 16.50 cm   | 12.33 cm <sup>2</sup> |
| Observed number of discs  | 46         | 4                     |

Table 63 Model Ee. Investigation of one set of discs randomly mixed among another set of discs.

|   | Right half | Left half             |
|---|------------|-----------------------|
| Area of each half sheet ( $A$ )   | 312.5 cm   | 312.5 cm              |
| True number of discs per half sheet ( $n$ )                                   | 16         | 16                    |
| Area of each disc ( $D$ )   | 2.01 cm    | 2.01 cm <sup>2</sup>  |
| Hypothetical mean variable free area $\frac{A}{n-1}$<br>minus $1.46 \times D$ | 17.90 cm   | 17.90 cm <sup>2</sup> |
| Observed mean variable free area  | 19.77 cm   | 17.15 cm <sup>2</sup> |
| Observed S. D. of individual var free area                                    | 11.90 cm   | 12.00 cm              |
| Observed number of discs  | 15         | 19                    |

Table 64 Model Gg. Investigation of one set of discs randomly mixed among another set of discs.

|  | Right half            | Left half               |
|--|-----------------------|-------------------------|
| Area of each half sheet ( <i>A</i> )   | 1,012.5 cm            | 1,012.5 cm <sup>2</sup> |
| True number of discs per half sheet ( )                                      | 59.5                  | 59.5                    |
| Area of each disc ( <i>D</i> )   | 2.01 cm <sup>2</sup>  | 2.01 cm <sup>2</sup>    |
| Hypothetical mean variable free area $\frac{A}{-1}$<br>minus $1.46 \times D$ | 14.37 cm              | 14.37 cm <sup>2</sup>   |
| Observed mean variable free area   | 13.34 cm <sup>2</sup> | 11.58 cm <sup>2</sup>   |
| Observed S. D. of individual var free area                                   | 13.59 cm <sup>2</sup> | 10.32 cm <sup>2</sup>   |
| Observed number of discs   | 53                    | 64                      |

Table 65. Model Fl. Investigation of one set of discs randomly mixed among another set of discs.

|  | Right half            | Left half             |
|--|-----------------------|-----------------------|
| Area of each half sheet ( <i>A</i> )   | 144.5                 | 144.5                 |
| True number of discs per half sheet ( )                                      | 11.5                  | 11.5                  |
| Area of each disc ( <i>D</i> )   | 2.01 cm               | 2.01 cm <sup>2</sup>  |
| Hypothetical mean variable free area $\frac{A}{-1}$<br>minus $1.46 \times D$ | 10.83 cm <sup>2</sup> | 10.83 cm <sup>2</sup> |
| Observed mean variable free area   | 7.80 cm               | 12.05 cm <sup>2</sup> |
| Observed S. D. of individual var free area                                   | 6.55 cm <sup>2</sup>  | 10.88 cm <sup>2</sup> |
| Observed number of discs   | 14                    | 9                     |

true number would, therefore, be somewhat less than 40 per cent. The disc centers marked set 1 would be randomly mixed with the non marked disc centers (set 2).

With two sets of randomly placed and randomly mixed discs, the mean variable free area around set 1 would be expected to take a value as if the discs of set 1 had been the only ones present. The S. D. (in the meaning of square root of the variance) of individual variable free areas around set 1 discs, would also be expected to take a value as if set 1 discs were the only ones present.

From tables 61—65 and fig 13 and 14 the observed S. D. of individual variable free area is seen to vary in the same direction as the observed mean variable free area, just as for one set of random discs. The value of the observed S. D. of the individual variable free area is generally found to be slightly smaller than the observed mean variable free area. The correlation is probably a linear one, the observed S. D. being in the neighborhood of 90 per cent of the value of the observed mean variable free area.

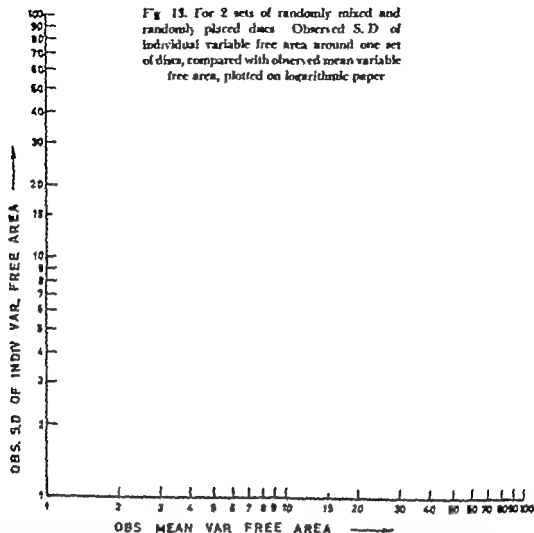


Fig 13. For 2 sets of randomly mixed and randomly placed discs. Observed S.D. of individual variable free area around one set of discs, compared with observed mean variable free area, plotted on logarithmic paper

c) *Observed mean variable free area compared with hypothetical value*

Tables 61--63 and fig 15 show the observed mean variable free areas as well as the hypothetical values. The observed value is lower than the hypothetical value in 8 out of 10 cases. This may be due to coincidence. Some of the differences between hypothetical and observed value seem to be rather large, notably for the left half of sheet Aa. The hypothetical mean variable free area in that case is

20.61 cm, whereas the observed value is only 19.19 cm. We want to know whether this difference is large enough to make our hypothesis unlikely. Because of its dependence of the mean variable free area, the standard deviation of the observed mean variable free area would not be an appropriate measure of this difference. The data might have been transformed to logarithms, but we have chosen not to do so.

If we on fig 14 compare the observed S.D. of individual variable free area in

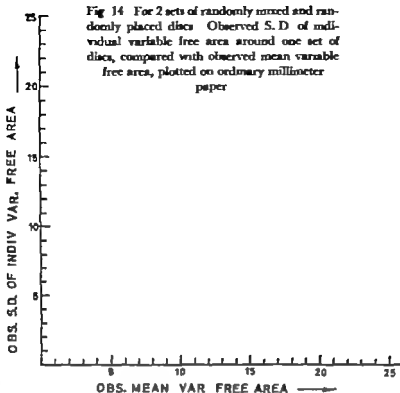


Fig 14 For 2 sets of randomly mixed and randomly placed discs. Observed S. D. of individual variable free area around one set of discs, compared with observed mean variable free area, plotted on ordinary millimeter paper

our 10 cases, with the observed mean free area, the former value is found to be on the average slightly more than 10 per cent lower. Our hypothetical mean variable free area for sheet Aa is 20.61 cm and the true number of disc centers is 44.5. We might then perhaps say that the expected S. D. of the mean variable free area would be about  $\frac{20.61 \text{ cm} \times 0.90}{\sqrt{44.5}}$

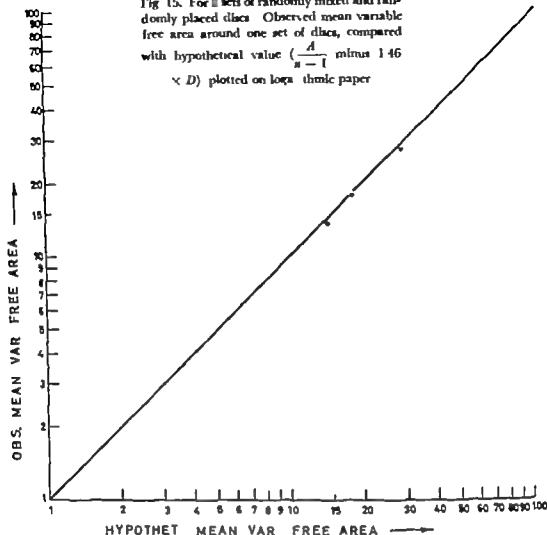
or 2.78 cm. The difference between hypothetical and observed value is  $20.61 - 13.19 = 7.42$  cm. Expressed in terms of the expected S. D. of the mean variable free area, it would be 2.67 S. D. This difference of 2.67 standard deviations, is well outside the 95 per cent probability limits. There are however 9 other values inside of these limits.

We did not think that the observed mean free areas came convincingly close to our hypothetical values. On the other hand we thought our hypothesis made good sense, and we did not want to abandon it just because one observation fell 2.67 standard deviations away and 8 out of 10 observations fell to one side of the hypothesis. If the observed S. D. for counts in equal divisions would fall close to our hypothetical value, we might perhaps dare to ascribe the deviations of the observed mean variable free area to chance.

d) *Hypothesis for relationship between mean variable free area, and S. D. for counts in equal divisions.*

With two sets of randomly distributed and randomly mixed discs, the mean variable

Fig. 15. For 11 sets of randomly mixed and randomly placed discs. Observed mean variable free area around one set of discs, compared with hypothetical value  $(\frac{A}{n-1} \text{ minus } 1.46 \times D)$  plotted on logarithmic paper



free area around set 1 is expected to take a value as if the discs of set 1 had been the only ones present. And, in keeping with this, our hypothesis is

$$\frac{\text{S.D. division count \#1 discs}}{\text{S.D. division count \#1 points}} = \frac{\text{mean variable free area \#1 discs}}{\text{mean free area \#1 points}}$$

$$\text{S.D. Poisson distrib} = \frac{1.46 \times D}{n_1 - 1} \times (1 - \frac{1}{n_1 - 1})$$

Of course the same adapting factors have to be applied as for a single set of discs (p. 44)

We counted disc centers belonging to set 1 in divisions sized 4 cm. in model Ff

Table 66. Observed S. D. of division counts for one of the two randomly distributed and randomly mixed sets of discs, compared to values predicted by our hypothesis.

|   | Observed and predicted S. D. as fraction of S. D. expected for a Poisson distrib. with the same mean. |      |                                |      |
|---|---|------|--------------------------------|------|
|   | Divisions 4 cm  |      | Divisions 6.25 cm <sup>2</sup> |      |
|   | Obs.  | Exp. | Obs.                           | Exp. |
| Model Hh<br>Area 2025.<br>Set 1 discs<br>no. 67 |   |      | 0.92                           | 0.93 |
| Model Aa<br>Area 2025<br>Set 1 discs<br>no. 89  |   |      | 0.92                           | 0.91 |
| Model Gg<br>Area 2025<br>Set 1 discs<br>no. 119 |   |      | 0.89                           | 0.88 |
| Model Ee<br>Area 625<br>Set 1 discs<br>no. 117  |   |      | 0.86                           | 0.90 |
| Model Ff<br>Area 256<br>Set 1 discs<br>no. 21   | 0.88  | 0.86 |                                |      |

and in divisions sized 6.25 cm<sup>2</sup> in the other 4 models. Table 66 shows the observed S. D. values in all cases to fall quite close to the values expected by our hypothesis, sometimes a trifle above, sometimes a trifle below.

### 3 Conclusions

1 Two sets of discs were assumed to be randomly mixed. If we, therefore, counted random samples of  $n$  discs regardless of set, the frequencies of getting 0, 1, 2, ...  $n$  discs from set 1 was given by expansion of the binomial  $(q + p)^n$  where  $q$  was probability of set 1 and  $p$  the probability of set 2. With other words, we would have a Bernoulli distribution.

2 Two sets of randomly placed and randomly mixed discs were thought to behave as if each set were alone. That is, when  $n_1$  discs from set 1 were placed in area  $A$  the mean variable area free of other set 1 discs, was thought to be  $\frac{A}{n_1 + 1}$  minus  $1.46 \times D$ .

3 The hypothesis previously set forth for relationship between variable free area and S. D. of count in equal divisions, was expected to be valid also for each one of two randomly mixed sets of discs. This would again imply that the discs would behave as if each set were alone. The hypothesis was

$$\frac{\text{S. D. divisions count } 1 \text{ discs}}{\text{S. D. divisions count } n_1 \text{ points}} = \frac{\text{mean var. free area of } n_1 \text{ discs}}{\text{mean free area of } n_1 \text{ points.}}$$

Adapting factors adapted the hypothesis to counts in smaller divisions.

This hypothesis was tested on 5 models containing two sets of randomly placed and randomly mixed discs. The observed values were in all cases found to fall quite close to the values expected by our hypothesis, sometimes a trifle above, sometimes a trifle below.

## C Reticulocytes in a smear

### 1 Previous work.

Several different techniques for reticulocyte counts are, or have been, in use. Each technique has, or has had its ardent supporters.

Some workers advocate the *direct reticulocyte count* where a known volume of blood is stained and diluted then counted in a counting chamber (12)

The majority of workers, however are using the *indirect reticulocyte count* counting e.g. 1 000 erythrocytes and recording the number of them containing a reticulum.

Many different techniques for indirect reticulocyte counts are employed

Some workers use a *wet preparation* allowing a small drop of blood to spread between a slide and a cover slip with or without sealing the edges to prevent evaporation (49 50 62 70 90) The reticulocyte stain is either introduced before the blood-stain mixture is spread between the slide and cover slip (49 62 70) or the slide has previously been covered by a thin film of stain (50 90)

Other workers make *dry preparations* either by smearing a drop of blood on a slide (10 15 22 40 62 67 68 78 79 95) or by allowing a small drop of blood to spread between two cover slips before separating them (23 62, 90) The reticulocyte stain is usually introduced before a drop of blood-stain mixture is smeared on a slide (10 15 22, 40 67 68, 78 79) or spread between cover slips (62) Sometimes a drop of blood is carefully smeared on a slide which has previously been covered by a thin film of stain (95) or a drop of blood is spread between cover slips previously covered by a thin film of stain (23 90)

With each of the different techniques

mentioned several different stains have been employed During the last few decades brilliant cresyl blue has been by far the most popular stain (10 22 23 40 49 50 62 67 68 70 78, 79 95) lately losing some ground to new methylene blue (12 14 66 94)

The standard deviation of one individual reticulocyte count will depend on the distribution of the reticulocytes. This distribution might possibly be more uniform with one technique than with another. The distribution might also differ in the hands of different workers, even if they follow the same technique.

Many workers performing indirect reticulocyte counts, find an observed standard deviation of one individual count corresponding at the best to a binomial distribution of the reticulocytes. Some of these workers have been using wet methods (50 62) some have been using dry smear methods (10 15 40 62) or a dry coverslip method (23 62)

Other workers, however have published observed standard deviations of an individual count corresponding to a reticulocyte distribution much more uniform than the binomial one (49 67 68 78) Their results are listed in table 2

These 4 authors employed techniques involving staining for some 20 minutes with a brilliant cresyl solution sometimes also an anticoagulant. Then thorough mixing and in 3 cases smearing on a slide in one case (49) using a wet method. In one case (68) counterstaining was performed with Giemsa stain, in the other cases no counterstaining was done. One author used silicized glassware (78) one paraffinized glassware (67) the other two just ordinary clean glassware (49 68, 70) It must now be strongly emphasized, that

not everyone using these techniques has found the same very uniform distribution of reticulocytes reported by these authors. Many workers using exactly the same techniques have failed to obtain smaller standard deviation than corresponding to a binomial distribution of the reticulocytes.

When a mixture of blood and staining fluid is left alone for 20 minutes, the reticulocytes, being lighter than the other erythrocytes, tend to concentrate in the top layer (51). It is, therefore, necessary that one mixes the sample thoroughly before making the smear either by stirring with a glass rod or by shaking a rubber stoppered tube. In other words, before this mixing the reticulocytes are generally assumed to be much less uniformly distributed in the blood sample than corresponding to a binomial distribution. Can it then be possible that thorough stirring or shaking of the sample will make the reticulocyte distribution become considerably more uniform than corresponding to a binomial distribution?

If we had been dealing with otherwise identical, black and white balls, it is generally appreciated that a distribution consistently more uniform than a binomial one could not be produced no matter how much shaking or mixing.

One way of explaining the departure from the binomial distribution might be by assuming some sort of repellent action between the reticulocytes, making each reticulocyte shun all others. I am not, however aware of any attempts to investigate the possibility of such a repellent action.

Of course there is another possible explanation for the exceptionally low standard deviations of individual reticulocyte counts, and that is unconscious bias on part of the person counting (p. 18)

## 2 Own work.

### a) *Own modified new-methylene blue method*

Preliminary investigations were done on mice, attempting to make reproducible reticulocyte counts. At first Seip's technique (78, 79) was employed, including the use of silicized glassware. In an attempt to reduce the unconscious bias as much as possible, the smears were un-marked and were put into blank envelopes which also contained hidden identification marks.

Duplicate counts from 3 different mice were done on the same day the person doing the count (the author) not knowing which smears were pairs. From a great many duplicate counts the S D of an individual count was calculated, and was found to be slightly larger than corresponding to a binomial distribution.

A very small drop of blood was used, in the beginning taken from the tail, later from the orbital plexus by means of a capillary hematocrit tube. While stirring the small sample of blood and staining fluid some admixture of silicone was inevitable making the distribution of erythrocytes in the smear appear somewhat uneven.

The erythrocyte distribution was to be as uniform as possible, for one thing because a Miller's ocular disc was to be employed in order to make counting less laborious (15 66 76). In an attempt to obtain a reliable staining as well as an even distribution of erythrocytes, our own technique was developed. A small drop of blood was allowed to touch a thick, ground coverglass close to one edge. The bend of a tiny smooth glass rod shaped like a hockey stick, was allowed to touch a small drop of 5 per cent new-methylene blue in 16 per cent potassium-ovalate. The stain adhering to the bent glass rod, about 1/10th the volume of the drop of



blood was mixed thoroughly with the blood for 30 seconds, by stirring with the glass rod along the lowermost 3 millimeter brim of the coverglass. Then a smear was made, and the slide immediately placed in a moist chamber for 20 minutes. At the end of the 20 minutes the smear was air dried and ready for counting. No counter staining was used. An oil immersion system giving a magnification of 800 was used, all counts were done by the author.

By keeping the volume of the stain down to only about 1/10th the volume of the blood the distribution of the erythrocytes would be as uniform as possible. It would of course have been possible to use a dried-stain method whereby an alcoholic solution of brilliant cresyl blue or Nile blue is smeared on a slide and air dried (95). A blood smear is subsequently smeared on top of the stain and the slide is immediately put in a moist chamber for 20 minutes before air drying. Such a method however is known to be rather unreliable when it comes to staining the reticulocytes.

It was hoped that our method would retain the efficient and reliable staining of the liquid stain methods, and at the same time have the most uniform erythrocyte distribution of the dried-stain methods.

As siliconized glassware was not used one might be afraid of losing some reticulocytes during the manipulations the stickiness of the reticulocytes being well known (24). Our method was, however, thought to involve a minimum of contact surfaces to which the reticulocytes might adhere. The mixing of stain and blood was done once only and over a very small area of the cover glass. During the process of smearing the mixture of blood and stain would have had to come in contact with about the same area of the cover glass, anyway.

#### b) *Method of counting and plotting reticulocytes*

Six reticulocyte smears were made within 15 minutes from each of two persons:  
1) PJS healthy male whose erythrocytes had previously been examined (table 30)  
2) A M., male with hereditary spherocytosis, around 20 per cent reticulocytes, a hemoglobin value of 14.6 g per 100 ml blood.

Three smears with a faultiness appearance were picked for each person. By gross inspection and low power microscopy an area without any gross defects was marked off. An origo from which to start was noted in each smear. Counts were performed with a Miller's ocular disc inserted into one ocular of our Zeiss Winkel Standard Mikroskope.

In most cases there was no doubt about a cell being a reticulocyte. When it came to the most mature reticulocytes, however, there would often be some doubt as to whether they should be called reticulocytes or not. We laid down certain criteria for reticulocytes, and tried to stick to these criteria in order to make the counts reproducible. Our minimum requirements for reticulocytes were: 1) Either three blue granules, no matter how small. These three granules would not always lie in the same plane of depth of the cell, and were therefore not necessarily visible at the same time. Fine focusing adjustments were, therefore, carried out continuously during the reticulocyte counts. 2) Or one blue thread rod or body with a length of at least 1/10th the diameter of the cell, plus one blue granule no matter how small.

When counting the normal blood (PJS) reticulocytes were counted in the large division erythrocytes in the small division. The origo of the smear was placed exactly underneath the left lower corner of the large division. After counting in this first

Table 67 (PJS III Retica) No. of reticulocytes per field in each of 3 counts, attempting to count exactly the same fields in each count.

| Field | Reticulocyte no. |    |    | Field | Reticulocyte no. |    |    |
|-------|------------------|----|----|-------|------------------|----|----|
|       | Count            |    |    |       | Count            |    |    |
|       | 1                | 2  | 3  |       | 1                | 2  | 3  |
| 1     | 2                | 2  | 2  | 31    | 2                | 2  | 2  |
| 2     | 4                | 5  | 5  | 32    | 2                | 2  | 2  |
| 3     | 5                | 5  | 5  | 33    | 1                | 0  | 0  |
| 4     | 1                | 2  | 2  | 34    | 3                | 3  | 3  |
| 5     | 3                | 3  | 3  | 35    | 3                | 2  | 3  |
| 6     | 1                | 2  | 2  | 36    | 2                | 2  | 2  |
| 7     | 1                | 1  | 1  | 37    | 2                | 2  | 2  |
| 8     | 0                | 2  | 2  | 38    | 1                | 1  | 1  |
| 9     | 4                | 4  | 4  | 39    | 2                | 3  | 3  |
| 10    | 0                | 1  | 1  | 40    | 3                | 3  | 3  |
| 11    | 1                | 1  | 1  | 41    | 1                | 1  | 1  |
| 12    | 1                | 1  | 1  | 42    | 2                | 2  | 2  |
| 13    | 2                | 2  | 2  | 43    | 1                | 2  | 2  |
| 14    | 3                | 3  | 3  | 44    | 2                | 2  | 2  |
| 15    | 1                | 1  | 1  | 45    | 1                | 2  | 2  |
| 16    | 2                | 2  | 2  | 46    | 1                | 2  | 2  |
| 17    | 1                | 2  | 2  | 47    | 1                | 1  | 1  |
| 18    | 3                | 4  | 4  | 48    | 0                | 0  | 0  |
| 19    | 1                | 1  | 1  | 49    | 1                | 1  | 1  |
| 20    | 2                | 2  | 2  | 50    | 2                | 2  | 2  |
| 21    | 1                | 2  | 2  | 51    | 1                | 1  | 1  |
| 22    | 2                | 2  | 2  | 52    | 3                | 3  | 3  |
| 23    | 0                | 0  | 0  | 53    | 1                | 1  | 1  |
| 24    | 0                | 0  | 0  | 54    | 3                | 3  | 3  |
| 25    | 0                | 0  | 0  | 55    | 1                | 1  | 1  |
| 26    | 0                | 0  | 0  | 56    | 2                | 2  | 2  |
| 27    | 0                | 0  | 0  | 57    | 3                | 3  | 3  |
| 28    | 3                | 3  | 3  | 58    | 4                | 4  | 4  |
| 29    | 0                | 1  | 1  | 59    | 3                | 3  | 3  |
| 30    | 5                | 5  | 5  | 60    | 0                | 0  | 0  |
| Total | 48               | 59 | 59 |       | 54               | 56 | 57 |

Table 68 (PJS IV Retica) No. of reticulocytes per field in each of 3 counts, attempting to count exactly the same fields in each count.

| Field | Reticulo-<br>cytes no. |    |    | Field | Reticulo-<br>cytes no. |    |    |
|-------|------------------------|----|----|-------|------------------------|----|----|
|       | Count                  |    |    |       | Count                  |    |    |
|       | 1                      | 2  | 3  |       | 1                      | 2  | 3  |
| 1     | 2                      | 1  | 2  | 31    | 3                      | 3  | 3  |
| 2     | 1                      | 1  | 1  | 32    | 0                      | 0  | 0  |
| 3     | 2                      | 2  | 2  | 33    | 2                      | 2  | 2  |
| 4     | 2                      | 2  | 2  | 34    | 1                      | 1  | 1  |
| 5     | 0                      | 1  | 1  | 35    | 3                      | 4  | 4  |
| 6     | 3                      | 3  | 3  | 36    | 3                      | 3  | 3  |
| 7     | 1                      | 1  | 1  | 37    | 3                      | 3  | 3  |
| 8     | 3                      | 2  | 2  | 38    | 1                      | 1  | 1  |
| 9     | 2                      | 2  | 2  | 39    | 0                      | 0  | 0  |
| 10    | 1                      | 1  | 1  | 40    | 0                      | 0  | 0  |
| 11    | 1                      | 1  | 1  | 41    | 1                      | 1  | 1  |
| 12    | 1                      | 1  | 1  | 42    | 3                      | 3  | 3  |
| 13    | 2                      | 2  | 2  | 43    | 3                      | 3  | 3  |
| 14    | 1                      | 1  | 1  | 44    | 2                      | 2  | 2  |
| 15    | 2                      | 3  | 3  | 45    | 4                      | 4  | 4  |
| 16    | 2                      | 2  | 2  | 46    | 0                      | 0  | 0  |
| 17    | 1                      | 1  | 1  | 47    | 2                      | 2  | 2  |
| 18    | 0                      | 0  | 0  | 48    | 1                      | 1  | 1  |
| 19    | 1                      | 1  | 1  | 49    | 0                      | 0  | 0  |
| 20    | 0                      | 0  | 0  | 50    | 1                      | 1  | 1  |
| 21    | 1                      | 1  | 1  | 51    | 1                      | 1  | 1  |
| 22    | 0                      | 0  | 0  | 52    | 0                      | 0  | 0  |
| 23    | 2                      | 2  | 1  | 53    | 3                      | 3  | 3  |
| 24    | 2                      | 2  | 2  | 54    | 2                      | 2  | 2  |
| 25    | 0                      | 0  | 0  | 55    | 2                      | 2  | 2  |
| 26    | 4                      | 4  | 4  | 56    | 0                      | 0  | 0  |
| 27    | 1                      | 1  | 1  | 57    | 2                      | 2  | 2  |
| 28    | 3                      | 3  | 3  | 58    | 0                      | 0  | 0  |
| 29    | 2                      | 2  | 2  | 59    | 0                      | 0  | 0  |
| 30    | 4                      | 4  | 4  | 60    | 2                      | 2  | 2  |
| Total | 47                     | 47 | 47 |       | 45                     | 46 | 46 |

division, the smear was moved vertically upwards exactly the width of one large division. In this way we proceeded until 10 consecutive large divisions were counted and then the counting was started over again exactly the width of one large division

lateral to the origin of the smear. Reticulocytes were in this manner counted in 60 large divisions, total erythrocytes in 60 small divisions. Blind control counts were done at a later date aiming to cover exactly the same divisions.

Table 69 (PJS VI Retica.) No. of reticulocytes per field in each of 3 counts, attempting to count exactly the same fields in each count.

| Field | Reticulo-<br>cyte no. |    |    | Field | Reticulo-<br>cyte no. |    |    |
|-------|-----------------------|----|----|-------|-----------------------|----|----|
|       | Count                 |    |    |       | Count                 |    |    |
|       | 1                     | 2  | 3  |       | 1                     | 2  | 3  |
| 1     | 2                     | 1  | 2  | 31    | 1                     | 1  | 1  |
| 2     | 3                     | 3  | 3  | 32    |                       | 2  |    |
| 3     | 2                     | 2  | 2  | 33    | 5                     | 5  | 5  |
| 4     | 2                     | 2  |    | 34    | 3                     | 3  | 2  |
| 5     | 3                     | 3  | 3  | 35    | 3                     | 3  | 3  |
| 6     | 2                     | 3  | 3  | 36    | 1                     | 1  | 1  |
| 7     | 2                     | 2  | 2  | 37    | 4                     | 4  | 4  |
| 8     | 1                     | 1  | 1  | 38    | 4                     | 4  | 4  |
| 9     |                       | 2  | 2  | 39    | 1                     | 2  | 2  |
| 10    | 2                     | 4  | 4  | 40    | 2                     | 1  | 1  |
| 11    | 0                     | 0  | 0  | 41    | 4                     | 4  | 4  |
| 12    | 2                     | 2  | 2  | 42    | 3                     | 3  | 3  |
| 13    | 3                     | 3  | 3  | 43    | 4                     | 4  | 4  |
| 14    | 4                     | 3  | 3  | 44    | 2                     | 2  | 2  |
| 15    | 3                     | 3  | 3  | 45    | 1                     | 1  | 1  |
| 16    | 3                     | 2  | 2  | 46    | 5                     | 5  | 5  |
| 17    | 1                     | 1  | 1  | 47    | 3                     | 3  | 3  |
| 18    | 3                     | 3  | 3  | 48    | 5                     | 5  | 5  |
| 19    | 2                     | 3  | 3  | 49    | 6                     | 5  | 6  |
| 20    | 5                     | 5  | 5  | 50    |                       | 2  | 3  |
| 21    | 3                     | 4  | 3  | 51    | 4                     | 4  | 4  |
| 22    | 2                     | 1  | 2  | 52    | 3                     | 3  | 3  |
| 23    | 2                     | 1  | 2  | 53    | 3                     | 2  | 3  |
| 24    | 4                     | 4  | 4  | 54    | 3                     | 3  | 3  |
| 25    | 3                     | 3  | 3  | 55    | 1                     | 0  | 0  |
| 26    | 2                     | 1  | 2  | 56    | 4                     | 5  | 5  |
| 27    | 1                     | 1  | 1  | 57    | 3                     | 3  | 3  |
| 28    | 0                     | 0  | 0  | 58    | 3                     | 3  | 3  |
| 29    | 2                     | 2  | 2  | 59    | 1                     | 1  | 1  |
| 30    | 2                     | 2  | 2  | 60    | 2                     | 2  | 2  |
| Total | 68                    | 67 | 70 |       | 88                    | 84 | 88 |

When counting the blood with reticulocytes (A. M.) reticulocytes as well as total erythrocytes were counted in the small division of the Miller's ocular disc. The origo in the smear was placed exactly underneath the left lower corner of the

Table 70 (A. M. I Retica.) No. of reticulocytes per field in each of 2 counts, attempting to count exactly the same fields in each count.

| Field | Reticulo-<br>cytes no. |     | Field | Reticulo-<br>cytes no. |     |
|-------|------------------------|-----|-------|------------------------|-----|
|       | Count                  |     |       | Count                  |     |
|       | 1                      | 2   |       | 1                      | 2   |
| 1     | 7                      | 7   | 31    | 8                      | 8   |
| 2     | 3                      | 4   | 32    | 5                      | 4   |
| 3     | 7                      | 6   | 33    | 2                      | 3   |
| 4     | 1                      | 1   | 34    | 3                      | 3   |
| 5     | 4                      | 4   | 35    | 3                      | 5   |
| 6     | 7                      | 8   | 36    | 0                      | 0   |
| 7     | 3                      | 2   | 37    | 3                      | 3   |
| 8     | 5                      | 5   | 38    | 6                      | 7   |
| 9     | 7                      | 6   | 39    | 5                      | 6   |
| 10    | 9                      | 8   | 40    | 3                      | 3   |
| 11    | 3                      | 3   | 41    | 5                      | 5   |
| 12    | 6                      | 5   | 42    | 5                      | 5   |
| 13    | 4                      | 4   | 43    | 4                      | 3   |
| 14    | 5                      | 4   | 44    | 1                      | 1   |
| 15    | 5                      | 4   | 45    | 5                      | 4   |
| 16    | 6                      | 7   | 46    | 6                      | 6   |
| 17    | 6                      | 6   | 47    | 5                      | 7   |
| 18    | 4                      | 5   | 48    | 9                      | 9   |
| 19    | 4                      | 4   | 49    | 3                      | 3   |
| 20    | 3                      | 4   | 50    | 6                      | 5   |
| 21    | 3                      | 3   | 51    | 4                      | 4   |
| 22    | 5                      | 5   | 52    | 5                      | 6   |
| 23    | 7                      | 7   | 53    | 4                      | 4   |
| 24    | 4                      | 4   | 54    | 2                      | 2   |
| 25    | 2                      | 2   | 55    | 4                      | 4   |
| 26    | 4                      | 4   | 56    | 5                      | 5   |
| 27    | 5                      | 5   | 57    | 4                      | 4   |
| 28    | 2                      | 2   | 58    | 6                      | 6   |
| 29    | 5                      | 5   | 59    | 7                      | 6   |
| 30    | 5                      | 5   | 60    | 3                      | 4   |
| Total | 143                    | 159 |       | 151                    | 155 |

small division. After counting this first division the smear was moved vertically upwards exactly the width of one small division. In this way we proceeded until 10 consecutive small divisions were counted, and then started over again exactly

Table 71. (A. M. II Reten.) No. of reticulocytes per field in each of 3 counts, attempting to count exactly the same fields in each count.

| Field | Reticulo-<br>cytes no. |     |     | Field | Reticulo-<br>cytes no. |     |     |
|-------|------------------------|-----|-----|-------|------------------------|-----|-----|
|       | Count                  |     |     |       | Count                  |     |     |
|       | 1                      | 2   | 3   |       | 1                      | 2   | 3   |
| 1     | 6                      | 6   | 6   | 31    | 6                      | 6   | 6   |
| 2     | 3                      | 3   | 3   | 32    | 3                      | 2   | 2   |
| 3     | 6                      | 5   | 6   | 33    | 2                      | 2   | 2   |
| 4     | 1                      | 1   | 1   | 34    | 3                      | 3   | 3   |
| 5     | 4                      | 3   | 3   | 35    | 5                      | 5   | 6   |
| 6     | 4                      | 5   | 5   | 36    | 5                      | 5   | 5   |
| 7     | 6                      | 7   | 7   | 37    | 3                      | 3   | 3   |
| 8     | 4                      | 7   | 6   | 38    | 9                      | 9   | 9   |
| 9     | 6                      | 7   | 7   | 39    | 2                      | 2   | 2   |
| 10    | 3                      | 4   | 3   | 40    | 6                      | 8   | 8   |
| 11    | 7                      | 6   | 7   | 41    | 4                      | 4   | 4   |
| 12    | 4                      | 4   | 4   | 42    | 7                      | 7   | 7   |
| 13    | 2                      | 2   | 2   | 43    | 6                      | 7   | 7   |
| 14    | 4                      | 5   | 5   | 44    | 6                      | 6   | 6   |
| 15    | 8                      | 8   | 8   | 45    | 3                      | 2   | 3   |
| 16    | 3                      | 3   | 3   | 46    | 7                      | 6   | 7   |
| 17    | 5                      | 5   | 5   | 47    | 1                      | 1   | 1   |
| 18    | 6                      | 7   | 6   | 48    | 7                      | 8   | 7   |
| 19    | 7                      | 7   | 7   | 49    | 3                      | 3   | 3   |
| 20    | 1                      | 2   | 1   | 50    | 6                      | 6   | 6   |
| 21    | 6                      | 5   | 6   | 51    | 3                      | 1   | 2   |
| 22    | 6                      | 6   | 7   | 52    | 8                      | 9   | 8   |
| 23    | 3                      | 3   | 3   | 53    | 6                      | 6   | 6   |
| 24    | 3                      | 3   | 3   | 54    | 4                      | 4   | 4   |
| 25    | 6                      | 5   | 5   | 55    | 8                      | 8   | 8   |
| 26    | 6                      | 6   | 6   | 56    | 4                      | 2   | 3   |
| 27    | 3                      | 3   | 3   | 57    | 4                      | 5   | 4   |
| 28    | 3                      | 4   | 4   | 58    | 6                      | 5   | 6   |
| 29    | 7                      | 6   | 6   | 59    | 6                      | 7   | 5   |
| 30    | 5                      | 8   | 8   | 60    | 7                      | 5   | 6   |
| Total | 138                    | 146 | 146 |       | 150                    | 147 | 149 |

Table 72. (A. M. V Reten.) No. of reticulocytes per field in each of 3 counts, attempting to count exactly the same field in each count.

| Field | Reticulo-<br>cytes no. |     |     | Field | Reticulo-<br>cytes no. |     |     |
|-------|------------------------|-----|-----|-------|------------------------|-----|-----|
|       | Count                  |     |     |       | Count                  |     |     |
|       | 1                      | 2   | 3   |       | 1                      | 2   | 3   |
| 1     | 5                      | 5   | 5   | 31    | 3                      | 2   | 3   |
| 2     | 2                      | 2   | 2   | 32    | 5                      | 5   | 5   |
| 3     | 3                      | 4   | 3   | 33    | 2                      | 3   | 2   |
| 4     | 2                      | 2   | 3   | 34    | 3                      | 3   | 3   |
| 5     | 3                      | 4   | 4   | 35    | 7                      | 8   | 8   |
| 6     | 5                      | 6   | 5   | 36    | 7                      | 5   | 6   |
| 7     | 2                      | 3   | 3   | 37    | 6                      | 7   | 7   |
| 8     | 4                      | 4   | 4   | 38    | 3                      | 4   | 3   |
| 9     | 3                      | 3   | 3   | 39    | 3                      | 1   | 1   |
| 10    | 3                      | 3   | 3   | 40    | 3                      | 4   | 3   |
| 11    | 3                      | 3   | 3   | 41    | 4                      | 4   | 4   |
| 12    | 4                      | 5   | 5   | 42    | 2                      | 2   | 2   |
| 13    | 3                      | 3   | 3   | 43    | 3                      | 3   | 3   |
| 14    | 3                      | 4   | 4   | 44    | 4                      | 6   | 4   |
| 15    | 5                      | 6   | 5   | 45    | 5                      | 5   | 5   |
| 16    | 3                      | 3   | 3   | 46    | 7                      | 7   | 7   |
| 17    | 4                      | 4   | 3   | 47    | 4                      | 3   | 4   |
| 18    | 2                      | 3   | 3   | 48    | 2                      | 3   | 2   |
| 19    | 1                      | 1   | 1   | 49    | 4                      | 5   | 4   |
| 20    | 4                      | 3   | 3   | 50    | 1                      | 2   | 1   |
| 21    | 7                      | 7   | 7   | 51    | 2                      | 2   | 2   |
| 22    | 4                      | 5   | 4   | 52    | 4                      | 4   | 5   |
| 23    | 6                      | 6   | 6   | 53    | 5                      | 6   | 6   |
| 24    | 3                      | 3   | 3   | 54    | 4                      | 5   | 4   |
| 25    | 7                      | 7   | 7   | 55    | 4                      | 6   | 4   |
| 26    | 8                      | 7   | 7   | 56    | 3                      | 3   | 3   |
| 27    | 7                      | 7   | 7   | 57    | 3                      | 3   | 3   |
| 28    | 3                      | 3   | 3   | 58    | 4                      | 5   | 4   |
| 29    | 4                      | 2   | 3   | 59    | 3                      | 3   | 2   |
| 30    | 5                      | 6   | 6   | 60    | 6                      | 5   | 4   |
| Total | 118                    | 124 | 121 |       | 118                    | 126 | 116 |

the width of one small division lateral to the origin of the smear. Reticulocytes as well as total erythrocytes, were in this manner counted in 60 small divisions. Blind control counts were done later aiming to cover exactly the same divisions

When two independent counts had been done, photographs were made of the areas counted. A third count was done afterwards, and each reticulocyte was identified during microscopy and marked on the photographs. During this third

Table 73 Total erythrocytes, total reticulocytes, and reticulocytes as per cent of total erythrocytes, for each of our 6 reticulocyte smears. Only count 1 is used.

| Retic smear | Total erythrocytes | Total retics. | Retics. as per cent |
|-------------|--------------------|---------------|---------------------|
| PJS III     | $1.062 \times 9$   | 102           | 1.03                |
| PJS IV      | $757 \times 9$     | 92            | 1.35                |
| PJS V I     | $1,292 \times 9$   | 156           | 1.51                |
| AM I        | 1,266              | 274           | 21.61               |
| AM II       | 1,248              | 288           | 23.08               |
| AM V        | 1,280              | 256           | 19.91               |

count the results of 1st and 2nd counts were accessible. The approximate position of each reticulocyte had during the two independent counts been plotted in relation to the respective division in order to facilitate later re-identification of the reticulocytes. The staining had for some reason faded in smear A M I after the photographs had been made. The third count as well as marking the reticulocytes on the photographs had therefore to be abandoned for that smear. Tables 67—72 list the reticulocyte count in each of the 60 divisions for 2 counts of smear A. M. I for 3 counts of the other 5 smears. Table 73 shows the total erythrocytes, total reticulocytes and per cent reticulocytes for each of our 6 smears. Only count 1 is used.

*Diameter measurements on reticulocyte smears.* Oil immersions on photographs were made of all 6 reticulocyte smears from the areas used for counting. The diameter of a number of erythrocytes were measured to give a mean erythrocyte diameter for each smear. The same procedure and the same measuring points were used as when measuring diameter in May-Grünwald & Giemsa (M-G & G) stained smears.

Table 74 Diameter of random total erythrocytes for 5 reticulocyte smears, and also diameter of random reticulocytes for 2 smears. Measurement unit is 1 "prototype  $\mu$ "

| Smear   | Mean diam. total erythrocytes | Mean diam. retic. |
|---------|-------------------------------|-------------------|
| PJS III | 7.1804                        |                   |
| PJS IV  | 7.2065                        |                   |
| PJS V I | 6.7578                        |                   |
| AM II   | 5.8029                        | 6.1948            |
| AM V    | 5.9510                        | 6.0834            |

The more greenish color of the reticulocyte preparation would be expected to make the cells appear slightly larger when photographed with white light, but probably not with our greenish filter (56).

Table 4 lists the mean diameter of randomly picked total erythrocytes in the 5 smears. For the two smears showing reticulocytosis, the mean diameter of randomly picked reticulocytes is also listed. The mean reticulocyte diameter is found to be respectively 1.0675 and 1.0222 times the diameter of the total erythrocytes, on the average 1.0449.

#### d) Observed S. D. of total erythrocyte division counts

When the PJS reticulocyte smears were counted, reticulocytes were counted in the large division and total erythrocytes in the small division of the Miller's ocular disc. None of the small divisions had a common border.

When the A. M. reticulocyte smears were counted, reticulocytes as well as total erythrocytes were counted in the small divisions. Two consecutive small divisions would therefore have a common border.

The S. D. of total erythrocyte division count was calculated in two different ways

Table 75. Observed S. D. of individual, total erythrocyte division count, compared with values predicted by our hypothesis for randomly placed discs. Observed and hypothetical S. D. is given as fraction of the S. D. expected for a Poisson distribution with the same mean.

| Retic. smear | Hypothetical S. D. | Observed S. D. |
|--------------|--------------------|----------------|
| PJS III      | 0.3682             | 0.5553         |
| PJS IV       | 0.5460             | 0.8268         |
| PJS VI       | 0.9299             | 0.6630         |
| AM II        | 0.5137             | 0.9539         |
| AM V         | 0.4816             | 0.8479         |

One way was by considering each division count to be one of 60 counts from the same sample. The other way was by the multiple difference method for the PJS smears the difference between divisions 1 and 2, 3 and 4 etc. and for the A. M. smears the difference between divisions 1 and 3, 2 and 4 etc. in order to avoid common borders.

The expected S. D. of individual division count of total erythrocytes was calculated by our hypothesis for ideal discs. In table 75 the observed S. D. of division counts is compared with the expected value. It is noticed that the observed S. D. is considerably higher than the hypothetical value, especially for the A. M. smears. If we look at a photograph of e.g. the A. M. V smear (fig. 21) we notice a suggestion of the net-like appearance previously described (p. 74). This tendency towards a net-like arrangement, is probably the reason why the erythrocyte distribution of the A. M. smears was so far from the hypothetical value. The observed erythrocyte distribution of the A. M. smears was actually only slightly more uniform than a Poisson distribution.

Also the PJS smears showed an erythrocyte distribution considerably less uni-

form than the hypothetical one, in contrast to the ordinary blood smears from PJS which had previously been investigated, tables 56-57.

#### c) Observed S. D. of reticulocyte division counts

The total erythrocytes were found to be much less uniformly distributed than randomly placed discs. The observed S. D. for division counts deviated only 1/2 to 1/4 as much from the S. D. of a Poisson distribution as was expected for randomly placed discs. If the reticulocytes are randomly mixed among the other erythrocytes, the S. D. of reticulocyte division counts would be expected to behave in a similar manner. When the total erythrocyte division count has an S. D. deviating 1/4 of the hypothetical deviation from the S. D. of a Poisson distribution the S. D. of a reticulocyte division count will also be expected to deviate only 1/4 of the hypothetical deviation, from the S. D. of a Poisson distribution.

When it comes to the 3 PJS smears, this created no problem at all. The reticulocytes were so far between, that there would hardly be any crowding effect. The hypothetical S. D. for reticulocyte division count was in all 3 cases 0.99  $\times$  the S. D. expected for a Poisson distribution with the same mean. If we take 1/2 of the hypothetical deviation from the Poisson S. D. we shall obtain an adjusted hypothetical S. D. of about 0.995  $\times$  the S. D. of a Poisson distribution which is essentially the same as the hypothetical S. D. before adjustment.

For the 2 A. M. smears the hypothetical S. D. for reticulocyte division counts was respectively 0.87 and 0.89 the S. D. of a Poisson distribution with the same mean. The S. D. of total erythrocytes deviated only about 1/4 of the hypothetical value from the S. D. of a Poisson distribution.

Table 76. Possible effect of a moderate systematic difference within a sample.

| Indiv<br>per div | Expected frequencies                              |                        |                        |                                  |
|------------------|---|------------------------|------------------------|----------------------------------|
|                  | No systematic<br>difference<br>60 div<br>mean 2.0 | Systematic difference  |                        |                                  |
|                  |   | 30 div<br>mean 1.7 (a) | 30 div<br>mean 2.3 (b) | Total 60 div<br>mean 2.0 (a + b) |
| 0                | 8.12010   | 5.4805                 | 3.00777                | 8.48829                          |
| 1                | 16.24026  | 9.31686                | 6.91785                | 16.23471                         |
| 2                | 16.24026  | 7.91934                | 7.95555                | 15.87489                         |
| 3                | 10.82682  | 4.48761                | 6.09924                | 10.58685                         |
| 4                | 5.41341   | 1.90723                | 3.50706                | 5.41431                          |
| 5                | 2.16534   | 0.61845                | 1.61325                | 2.26170                          |
| 6                | 0.72180   | 0.18372                | 0.61842                | 0.80214                          |
| 7                | 0.20622   | 0.04461                | 0.20319                | 0.24780                          |
| 8                | 0.05154   | 0.00948                | 0.03841                | 0.06789                          |
| 9                | 0.01146   | 0.00180                | 0.01494                | 0.01674                          |
| 10               | 0.00278   | 0.00030                | 0.00342                | 0.00372                          |
| 11               | 0.00042   | 0.00006                | 0.00072                | 0.00078                          |
| 12               | 0.00006   |                        | 0.00015                | 0.00015                          |
| 13               |   |                        | 0.00003                | 0.00003                          |

If we take 1/4 of the deviation of the reticulocyte S.D. we shall for both smears get an adjusted hypothetical S.D. of about 0.97—the S.D. of a Poisson distribution with the same mean.

For each of the 60 reticulocyte smears reticulocytes were counted in each of 60 equal divisions. Only the results of the 1st count of 1 smear were used for calculating observed S.D. of division count.

The observed frequency of divisions having 0.1 reticulocytes was compared with the frequency expected for a Poisson distribution with the same mean (69). A small systematic difference between the two halves of a smear will probably not create any difficulties for this comparison. Assuming that there is no systematic difference and the mean number of reticulocytes per division is 2.0 the expected frequency of 0.1

is listed in table 76. Assume then a systematic difference 30 divisions having a mean of 1.7 reticulocytes per division and 30 having a mean of 2.3. The expected frequency of 0.1  $\times$  for the total 60 divisions is also given in table 76, and is seen to differ only insignificantly from the frequencies expected with no systematic difference.

In table 77—82 the observed frequencies of divisions having 0.1  $\times$  reticulocytes are compared with the frequencies expected for a Poisson distribution with the same mean. The observed frequencies fit fairly well with the expected values, except for smear A. M. II. This way of comparing observed frequencies with the frequencies expected for a Poisson distribution by means of a Goodness of fit table, is, however, known to be rather insensitive (3).

Table 77 (PJS III Retic.) Observed frequency of divisions with 0, 1  $\times$  reticulocytes, compared to the frequency expected for Poisson distribution.

| Retic. per div | Obs. freq. | Exp. freq. | Measure of Divergence |
|----------------|------------|------------|-----------------------|
| 0              | 10         | 10.96104   | 0.08                  |
| 1              | 20         | 18.63372   | 0.10                  |
| 2              | 15         | 15.83868   | 0.04                  |
| 3              | 10         | 8.97522    | 0.12                  |
| 4              | 3          | 5.59134    | 0.06                  |
| 5              | 2          |            |                       |
| more           |            |            |                       |
|                | 60         | 60.00000   | 0.40<br>= 3           |

Table 78. (PJS IV Retic.) Observed frequency of divisions with 0, 1  $\times$  reticulocytes, compared to the frequency expected for Poisson distribution.

| Retic. per div | Obs. freq. | Exp. freq. | Measure of Divergence |
|----------------|------------|------------|-----------------------|
| 0              | 14         | 13.38780   | 0.03                  |
| 1              | 16         | 20.08170   | 0.63                  |
| 2              | 17         | 15.06126   | 0.25                  |
| 3              | 10         | 11.46918   | 0.20                  |
| 4              | 3          |            |                       |
| more           |            |            |                       |
|                | 60         | 59.99994   | 1.31<br>= 2           |

The observed S. D. of individual division count was also calculated. This was done in two ways. One way was by considering each division count to be one of 60 counts from the same sample using for

$$\text{formula } S.D. = \sqrt{\frac{S_n(x - \bar{x})^2}{n - 1}}$$

Table 79 (PJS V Retic.) Observed frequency of divisions with 0, 1  $\times$  reticulocytes, compared to the frequency expected for a Poisson distribution.

| Retic. per div | Obs. freq. | Exp. freq. | Measure of Divergence |
|----------------|------------|------------|-----------------------|
| 0              | 2          | 4.45644    | 1.58                  |
| 1              | 9          | 11.58666   |                       |
| 2              | 19         | 15.06270   | 1.03                  |
| 3              | 17         | 13.05432   | 1.20                  |
| 4              | 8          | 8.48532    | 0.03                  |
| 5              | 4          | 7.35456    | 0.75                  |
| 6              | 1          |            |                       |
| more           |            |            |                       |
|                | 60         | 60.00000   | 4.59<br>= 3           |

Table 80. (A. M. I Retic.) Observed frequency of divisions with 0, 1  $\times$  reticulocytes, compared to the frequency expected for Poisson distribution (with mean 4.6)

| Retic. per div | Obs. freq. | Exp. freq. | Measure of Divergence |
|----------------|------------|------------|-----------------------|
| 0              | 1          | 0.60312    | 0.78                  |
| 1              | 2          | 2.77428    |                       |
| 2              | 4          | 6.38088    | 0.00                  |
| 3              | 10         | 9.78408    |                       |
| 4              | 11         | 11.25168   | 0.01                  |
| 5              | 16         | 10.35150   | 3.08                  |
| 6              | 7          | 7.93620    | 0.11                  |
| 7              | 8          | 5.21320    | 0.12                  |
| 8              | 1          | 5.70306    | 1.28                  |
| 9              | 2          |            |                       |
| more           |            |            |                       |
|                | 60         | 60.00000   | 5.58<br>= 5           |

The other was by the multiple difference method, from the difference between the counts in divisions 1 and 2, 3 and 4 etc.



Table 81 (A. M. II Retic.) Observed frequency of divisions with 0, 1  $\times$  reticulocytes, compared to frequency expected for a Poisson distribution.

| Retic. per div | Obs. freq | Exp. freq | Measure of Divergence |
|----------------|-----------|-----------|-----------------------|
| 0              | 0         | 0.49300   | 0.76                  |
| 1              | 3         | 2.37018   |                       |
| 2              | 3         | 5.68813   | 1.67                  |
| 3              | 13        | 9.10146   |                       |
| 4              | 9         | 10.92174  | 0.31                  |
| 5              | 4         | 10.48188  | 4.01                  |
| 6              | 17        | 8.38788   | 8.84                  |
| 7              | 7         | 5.75172   | 0.27                  |
| 8              | 3         |           | 1.15                  |
| 9              | 1         | 6.79998   |                       |
| more           |           |           |                       |
|                | 60        | 60.00006  | 17.04<br>$\approx 5$  |

Table 82. (A. M. V Retic.) Observed frequency of divisions with 0, 1  $\times$  reticulocytes, compared to frequency expected for a Poisson distribution (with mean 3.9)

| Retic. per div | Obs. freq | Exp. freq | Measure of Divergence |
|----------------|-----------|-----------|-----------------------|
| 0              | 0         | 1.21451   | 2.62                  |
| 1              | 2         | 4.73658   |                       |
| 2              | 8         | 9.23640   | 0.17                  |
| 3              | 11        | 12.00732  | 3.00                  |
| 4              | 14        | 11.70714  | 0.45                  |
| 5              | 8         | 9.13158   | 0.14                  |
| 6              | 3         | 3.93550   | 1.45                  |
| 7              | 6         |           | 0.16                  |
| 8              | 1         | 6.03102   |                       |
| more           |           |           |                       |
|                | 60        | 60.00006  | 7.99<br>$\approx 5$   |

Table 83 Observed S. D. of individual reticulocyte division count, compared with values predicted by our hypothesis, and our adjusted hypothesis, for sets of randomly placed and randomly mixed discs. Observed and predicted S. D. is given as fraction of the S. D. expected for a Poisson distribution with the same mean.

| Retic. mean | Hypothet. S. D. | Adjusted hypothet. S. D. | Observed S. D.     |                    |
|-------------|-----------------|--------------------------|--------------------|--------------------|
|             |                 |                          | Mult. diff. method | Same sample method |
| PJS III     | 0.99            | 0.975                    | 1.04               | 0.96               |
| PJS IV      | 0.99            | 0.995                    | 1.01               | 0.91               |
| PJS V I     | 0.99            | 0.993                    | 0.76               | 0.79               |
| AM II       | 0.87            | 0.97                     | 1.03               | 0.88               |
| AM V        | 0.89            | 0.97                     | 0.72               | 0.82               |

The results are listed in table 83. The observed S. D. of individual reticulocyte division count is given as a fraction of the S. D. expected for a Poisson distribution with the same mean. It is seen that the

observed S. D. in 3 cases comes quite close to the adjusted hypothetical S. D. for 2 sets of discs, but in 2 cases tends to be somewhat smaller.

*f) Mean variable free area around reticulocytes measured on photos.*

During the 3rd count, each reticulocyte was identified in the microscope and marked on the photographs. The center of each reticulocyte was marked by piercing the center of a circle drawn on roentgen film, the borders being carefully placed to match the erythrocyte border. The distance to the closest neighbor reticulocyte was measured, from each of the reticulocytes located in the central part of the area counted and photographed. Measurements were made from the center of each reticulocyte to the center of the closest neighbor reticulocyte, by means of our Castell ruler with unit 1.2 millimeter.

Table 84 shows the observed distance to the closest reticulocyte neighbor, the observed reticulocyte-free area and the observed mean reticulocyte-free area, for the 5 photographed reticulocyte smears.

In table 86 we have used the observed mean reticulocyte diameter for each of the two A.M. smears to calculate the non-variable, innermost  $\pi \cdot \left(\frac{\text{Diameter}}{2}\right)^2$  area. This innermost non-variable area is subtracted from the observed mean reticulocyte-free area, to give the observed mean variable reticulocyte-free area.

For the 3 PJS smears we did not measure the reticulocyte diameter only the diameter of the total erythrocytes. To obtain an approximate reticulocyte diameter for the 3 PJS smears, the observed diameter of total erythrocytes was multiplied with 1.0449 the factor found for the person A.M. with hereditary spherocytosis. Although the reticulocyte diameter in hereditary spherocytosis as well as in normal persons is known to be slightly larger than the diameter of the total erythrocytes, the ratio between reticulocyte and total diameter is not necessarily the same. This might cause slight

inaccuracy of the reticulocyte diameter used in our formulae for the PJS smears. In these 3 smears the reticulocytes were quite scanty however and their diameter would, therefore be rather unimportant in our formulae. If the reticulocyte diameter in our formulae increased or decreased by e.g. 20 per cent, the mean variable free area as well as the S. D. of division counts would remain practically unchanged.

If the reticulocytes had been distributed according to our hypothesis for two sets of randomly placed and randomly mixed discs, the S. D. of reticulocyte division counts would have been only slightly smaller than for a Poisson distribution. The distribution of the total erythrocytes caused us to adjust our expectations for the S. D. of reticulocyte division counts towards still closer agreement with the S. D. of a Poisson distribution. For the PJS smears this adjustment was quite negligible, and for the A.M. smears it was also quite small.

If a distribution is less uniform than a random distribution of discs, the S. D. of division counts will be higher and the mean variable free area smaller.

The negligible adjustment of the expected S. D. for the PJS smears would not cause us to expect any deviation from the hypothetical mean variable free area. The slight increase in expected S. D. of reticulocyte division counts for the A.M. smears, would make us expect a mean variable free area slightly smaller than the value calculated from our hypothesis for 2 sets of randomly placed and randomly mixed discs.

In tables 85 & 86 the observed mean variable reticulocyte-free area is compared to the area expected from our formula for two sets of randomly distributed discs. For the 3 PJS smears the observed mean

Table 84 Distance to closest neighbor for random reticulocytes in 5 different smears. Each smear photographed on a different day the A. M. smears with larger magnification than the PJS smears. Unit =  $\frac{1}{2}$  millimeter measurements on photographs.

| Distance            | Reticulocyte smear |                  |        |                  |        |                  |       |                    |      |                  |
|---------------------|--------------------|------------------|--------|------------------|--------|------------------|-------|--------------------|------|------------------|
|                     | PJS III            |                  | PJS IV |                  | PJS VI |                  | AM II |                    | AM V |                  |
|                     | No.                | Free area<br>No. | No.    | Free area<br>No. | No.    | Free area<br>No. | No.   | Free area<br>x No. | No.  | Free area<br>No. |
|                     |                    |                  | 2      | 25.14            |        |                  |       |                    |      |                  |
| 3                   | 6                  | 169.62           | 4      | 113.06           |        |                  |       |                    |      |                  |
| 4                   | 2                  | 100.50           | 2      | 100.5            | 4      | 201.0            |       |                    |      |                  |
| 5                   |                    |                  | 6      | 471.12           | 2      | 157.04           |       |                    |      |                  |
| III                 | 5                  | 563.50           | 3      | 339.3            | 3      | 339.3            |       |                    | 2    | 226.2            |
| 7                   | 2                  | 307.80           | 2      | 307.8            | 3      | 461.7            | 1     | 155.9              | 13   | 2,000.7          |
| 8                   |                    |                  |        |                  |        |                  | 45    | 9,045              | 22   | 4,422.0          |
| 9                   | 5                  | 1,272.5          |        |                  | 2      | 509.0            | 8     | 2,036              | 13   | 3,308.5          |
| 10                  | 1                  | 314.2            | 3      | 912.6            | 3      | 91.6             | 10    | 3,142              | 5    | 1,571            |
| 11                  | 5                  | 1,900.5          |        |                  | 5      | 1,900.5          | 5     | 1,900.5            | 1    | 380.0            |
| 12                  | 2                  | 904.8            | 8      | 3,619.2          | 5      | 2,262            |       |                    | 5    | 1,557.2          |
| 13                  |                    |                  |        |                  | 2      | 1,061.8          | 2     | 1,061.8            | 7    | 3,716.3          |
| 14                  | 1                  | 615.8            | 3      | 1,847.4          | 8      | 4,926.4          | 3     | 1,847.4            | 10   | 6,158            |
| 15                  | 6                  | 4,240.8          | 8      | 5,654.4          | 2      | 1,413.6          | 1     | 706.8              | 5    | 1,204            |
| III                 | 3                  | 2,412.3          | 2      | 1,608.2          | 1      | 804.1            | 2     | 1,608.2            | 10   | 8,041            |
| 17                  | 3                  | 2,723.4          | 1      | 907.8            | 2      | 1,815.6          | 2     | 1,815.6            | 4    | 3,631.2          |
| 18                  |                    |                  | 4      | 4,068            |        |                  | 3     | 3,051              | 8    | 8,136            |
| 19                  |                    |                  | 1      | 1,131            | 1      | 1,134            | 4     | 4,536              | 2    | 2,268            |
| 20                  |                    |                  |        |                  | 1      | 1,257            | 4     | 5,028              | 1    | 1,257            |
| 21                  |                    |                  | 3      | 4,158            |        |                  |       |                    | 4    | 5,544            |
| 22                  |                    |                  |        |                  | 1      | 1,320            | 3     | 4,560              | 1    | 1,320            |
| 23                  |                    |                  | 1      | 1,662            | 1      | 1,662            |       |                    | II   | 5,324            |
| 24                  |                    |                  | 2      | 3,609            |        |                  | 1     | 1,809              | 1    | 1,809            |
| 25                  | 1                  | 1,963            | 1      | 1,963            |        |                  | 1     | 1,963              |      |                  |
| 26                  | 1                  | 2,123            |        |                  |        |                  |       |                    |      |                  |
| 27                  |                    |                  |        |                  |        |                  |       |                    |      |                  |
| 28                  |                    |                  |        |                  |        |                  |       |                    |      |                  |
| 29                  | 1                  | 2,642            | 1      | 2,642            |        |                  |       |                    | 1    | 2,642            |
| 30                  |                    |                  |        |                  |        |                  |       |                    | 1    | 2,827            |
| 31                  |                    |                  |        |                  | 1      | 3,018            |       |                    | 1    | 3,018            |
| 32                  |                    |                  | 1      | 3,217            |        |                  |       |                    |      |                  |
| Total no.           | 44                 |                  | 38     |                  | 47     |                  | 95    |                    | 113  |                  |
| Total free area     |                    | 22,235.72        |        | 38,389.54        |        | 25,385.64        |       | 44,264.20          |      | 69,277.50        |
| Obs. mean free area |                    | 505.8118         |        | 661.8886         |        | 540.1200         |       | 465.9389           |      | 602.413          |

Table 85. Observed mean variable reticulocyte-free area around reticulocytes, compared with hypothetical value. Unit  $\frac{1}{2}$  millimeter measurements on photographs.

|  | Retic. smear |        |        |
|--|--------------|--------|--------|
|  | PJS III      | PJS IV | PJS VI |
| Area of smear (A)  | 22,100       | 38,304 | 22,200 |
| No. of retics.   | 41           | 58     | 47     |
| Area of each retic. (D)  | 3.673        | 3.6738 | 3.2289 |
| Hypothetical mean variable free area<br>( $\frac{A}{-1}$ minus $1.46 \times D$ ) | 508.66       | 666.64 | 477.89 |
| Obs. mean var. free area   | 491.30       | 647.19 | 527.20 |

Table 86. Observed mean variable reticulocyte-free area around reticulocytes, compared with hypothetical value. Unit is  $\frac{1}{2}$  millimeter measurements on photographs.

|   | Retic. smear  |            |
|---|---------------|------------|
|   | A. & L.<br>II | A. M.<br>I |
| Area of smear (A)   | 38,700        | 55,160     |
| No. of retics.  | 85            | 115        |
| Area of each retic. (D)   | 99.4161       | 38.3332    |
| Hypothetical mean variable<br>free area ( $\frac{A}{-1}$ minus $1.46$<br>$\times D$ ) | 354.13        | 427.60     |
| Obs. mean var. free area  | 308.27        | 448.27     |

variable free area is scattered around the hypothetical value, in two cases slightly below in one case slightly above the hypothetical value. For the 2 A. M. smears one observed mean variable free area is slightly above, the other value somewhat more below the hypothetical value for 2 sets of randomly distributed and randomly mixed discs.

### 3 Discussion

Experimental work related in previous chapters, has rendered likely some hypo-

theses regarding the distribution of randomly distributed discs.

In the present chapter the hypotheses for the distribution of two sets of randomly distributed and randomly mixed discs, were tested on reticulocytes in a smear.

Our own method of preparing a reticulocyte smear was developed aiming at a maximum efficiency of staining combined with the most uniform distribution of erythrocytes. In our experimental work, each reticulocyte smear was always to be considered as a separate sample. Whether our method gives reproducible results in duplicate preparations, is therefore a question outside the limits of the present investigation.

Comparing 1st and 2nd count in tables 67-72, is of considerable interest. These two counts were completely independent of each other and they were performed by the same person, under what was thought to be identical conditions. The number of reticulocytes found in one particular division, at times differs in the two counts. It is obvious that the difference between the two counts is much greater for reticulocytes than for erythrocytes, see table 53. This is to be expected. When it comes to reticulocyte counts, there is often difficulty in deciding whether a cell is a

reticulocyte or not. This difficulty comes in addition to the problem of allocating a given cell to the correct division a problem shared with ordinary erythrocyte counts.

In one single case (PIS III) considerably more reticulocytes were found in the 2nd and the 3rd, than in the 1st count. This was the first of our 6 reticulocyte smears to be counted, and it is a possibility that each division was scrutinized more thoroughly during the 2nd and 3rd count.

In one case (A. M. II) there was an excess of divisions containing 6 reticulocytes during the 1st count and very few divisions containing 5 reticulocytes. During the 2nd count it was rather the other way around. The explanation of this discrepancy might be that the author remembered the excessively many divisions containing 6 reticulocytes during the 1st count and therefore, during the 2nd count unconsciously tended to find more divisions with 5 reticulocytes and less with 6. This possibility was one of the reasons why the distribution of cells always was evaluated from the first count, the 2nd count being used merely for controlling the accuracy of the counting. The 3rd count used for marking the reticulocytes on photographs, was partly based on 1st and 2nd count.

The observed S. D. of individual, total erythrocyte counts, was found to be considerably higher than the hypothetical value for randomly distributed discs. This was especially marked for the A. M. smears. Close examination of these smears showed a suggested net like arrangement of the erythrocytes, probably the main reason for the large deviation from the hypothetical S. D. (fig. 21). The total erythrocytes in the reticulocyte smears from PJS, were also less uniformly distributed than the erythrocytes in the ordi-

nary blood smears from that person previously investigated. Mixing 9 parts of blood with 1 part of 5 per cent new methylene blue might have caused the erythrocytes in the reticulocyte smear to be less uniformly distributed.

If the reticulocytes are randomly mixed among the other erythrocytes, the S. D. of reticulocyte division counts would be expected to behave in a manner similar to the total erythrocytes. When the total erythrocyte division count has an S. D. deviating only 1/4 of the hypothetical deviation from the S. D. of a Poisson distribution, the S. D. of a reticulocyte division count would also be expected to deviate only 1/4 of the hypothetical deviation from the S. D. of a Poisson distribution.

In this way the hypothetical S. D. of reticulocyte division counts were adjusted, the S. D. of all 3 PJS smears becoming  $0.995 \times$  S. D. of a Poisson distribution and the adjusted hypothetical S. D. of the 2 A. M. smears being about  $0.97 \times$  Poisson S. D.

Table 83 shows that the observed S. D. of individual reticulocyte division counts for 3 of the smears came quite close to the adjusted hypothetical value. In the other 2 cases the observed S. D. tended to be somewhat smaller than the adjusted hypothetical value. The deviations from the adjusted hypothetical values were not large but both went in the same direction. Could some unconscious bias have affected the counts in such a direction as to give this unexpectedly low observed S. D.? If the counts were done by a mechanical robot the same amount of scrutinizing would be done in a division in which 7 reticulocytes are observed right away as in a division in which no reticulocytes are observed at first. When a human being is doing the counts, however he might conceivably use more effort trying to find

reticulocytes in divisions with a low number than in divisions with a high number of reticulocytes thus equalizing the counts and creating a too low observed S. D. of division counts. Although we were aware of this danger during our counts, we might still unconsciously have biased our counts in this manner.

One more reason for believing in such an unconscious bias, is the fact that the observed mean variable reticulocyte free areas fitted nicely with our hypothetical values. It must be kept in mind, that even if there would be an unconscious equalization of division counts, the distance to the closest reticulocyte neighbor would hardly be biased. For one thing it would be almost impossible to know during the marking of reticulocytes, what the observed mean variable free area was going to be.

### Conclusions.

1. Our own method of preparing a reticulocyte smear was developed, aiming at a maximum efficiency of staining combined with the most uniform distribution of erythrocytes.

2. The observed S. D. of individual total erythrocyte division counts, was found to be considerably higher than the hypothetical value for randomly distributed

discs. In the smears from subject A. M. this high observed S. D. was probably caused by a tendency towards a net-like arrangement of the erythrocytes.

If the reticulocytes are randomly mixed among the other erythrocytes, the S. D. of reticulocyte division counts would be expected to behave in a similar manner to the S. D. of the total erythrocyte division counts. The hypothetical S. D. of reticulocyte division counts was adjusted accordingly.

The observed S. D. of individual reticulocyte division counts was compared with the adjusted hypothetical S. D. for two sets of randomly placed and randomly mixed discs. In 3 instances the observed S. D. came quite close to the adjusted hypothetical value. In the other 2 instances the observed S. D. tended to be slightly smaller than the adjusted hypothetical value. Unconscious equalization might possibly account for these slight deviations on the low side of the adjusted hypothetical S. D.

3. The observed mean variable free area around reticulocytes was compared with the area expected according to our hypothesis for two sets of randomly placed and randomly mixed discs. The observed mean variable free area came quite close to the hypothetical area.

## General summary

I A general survey is given of the literature dealing with the distribution of erythrocytes in a counting chamber. The lack of investigations regarding the distribution of erythrocytes in a blood smear is pointed out.

A general survey is given of the literature dealing with the distribution of reticulocytes in a wet or dry preparation. Different authors represent rather opposing views on the distribution of reticulocytes. Some claim that reticulocytes are randomly mixed among the other erythrocytes and that the S. D. of reticulocyte count therefore will correspond to the S. D. of a binomial distribution. Other authors state that the reticulocytes are much more uniformly distributed as expressed by their own very low observed S. D. of reticulocyte counts.

This leads up to the outline of our present research problem, which falls naturally into two parts.

1 An attempt to find a mathematical expression for a random distribution of one set of discs. And then an attempt to find out if erythrocytes in a blood smear follow this distribution.

2 An attempt to find a mathematical expression for the distribution of  $n$  sets of randomly placed and randomly mixed discs. And then attempting to find out if reticulocytes in a smear follow this distribution.

II The free area around a point was defined and the value of the mean free area of a random distribution of points was developed theoretically. Models of randomly distributed points were constructed on sheets of millimeter paper by means of a coordinate system, and a table of random numbers. The observed mean free area on each model was found to agree well with the value theoretically developed.

The variable free area around discs was defined and a hypothesis was developed for the value of the mean variable free area of a random distribution of discs.

Models of randomly distributed discs were constructed on sheets of millimeter by means of a coordinate system, a table of random numbers, and a pair of compasses. The observed mean variable free area on each model was found to agree well with the hypothetical value.

When discs were counted in equal divisions, the S. D. of the individual division count was a certain fraction of the S. D. of a Poisson distribution with the same mean. The percentage deviation from the S. D. of a Poisson distribution was found to increase with increased size of the divisions.

A hypothesis was developed for the relationship between variable free area and S. D. for counts in equal divisions. This hypothesis was thought to be valid for counts in really large divisions. Adapting

factors were however calculated from the disc radius and the division sides, and adapted the hypothesis for use with divisions of any size.

The observed S. D. of division counts was found to agree well with the values given by the hypothesis with adapting factors.

Turner & Eadie as well as Watanabe have ventured on a theoretical model for randomly distributed discs. This model was found to give consistently too large S. D. of individual division count, compared with observed values.

The hypotheses developed for randomly distributed discs, had been found to agree well with observations on our models constructed on sheets of millimeter paper. It was then proceeded to find out if the hypotheses for randomly distributed discs would describe the distribution of erythrocytes in a smear equally well.

Several problems arose when the hypotheses, developed for discs, were to be tested on erythrocytes in a smear. At various stages of the diameter measurements, three different decisions or choices of procedure had to be made, each of which might influence the value of the observed diameter.

1) The diameters could be measured in a wet or a dry preparation. We chose to measure the diameter in a dry preparation. The diameter thus measured might be too low or too high depending upon the direction of a possible change in diameter during smearing and drying. It was thought that a possible change in erythrocyte diameter during smearing or air drying would largely take place before the position of each cell had become fixed. For this reason the mean erythrocyte diameter in the dry preparation was thought to be as appropriate to use in our formulae or even more appropriate, than the diameter in the wet preparation.

2) The photographs could be made with oil immersion, or with dry lens system. We chose to use oil immersion, for one thing because the magnification of the photographs would be larger and the diameters therefore easier to measure. If a dry lens system had been used, a larger erythrocyte diameter would have been obtained.

3) The point of the erythrocyte from which to measure, also had to be decided upon. We chose to measure the diameter from the outer edge of the dark borderline on one side of the erythrocyte to the outer edge on the other side. For one thing this point was the only one sharply defined. If we had measured e.g. from the inner edge on one side to the outer edge on the other side a smaller erythrocyte diameter would have been measured.

Some smears were made from diluted, others from undiluted, blood. The erythrocytes in our smears made from diluted blood, seemed to have shrunk somewhat, and their diameter was smaller. This shrinkage probably had occurred during dilution, and it was the shrunken erythrocytes which were thought to concern the distribution in a smear. The mean erythrocyte diameter observed in an area of a smear was therefore always the diameter to be used in the hypothetical formula for disc distributions.

Our micrometer scale was calibrated and the calibration was found to vary from part to part of the scale. This was in keeping with Ponder's warning about not accepting the micrometer scales at the maker's valuation. All our measurements therefore referred to one particular portion of the scale, called the "prototyp portion".

The distance from the center of each erythrocyte to that of the closest neighbor was measured on photographs, and the



observed mean variable free area was obtained. This observed mean variable free area was found to agree well with the hypothetical value for randomly placed discs.

Erythrocytes were counted in equal divisions to obtain the observed S. D. of division counts. The observed S. D. of division counts was found to agree well with the values given by our hypothesis for randomly placed discs, with adapting factors.

III It has previously been shown that if each of two independent events is following the Poisson distribution the sum of the two events will also follow the Poisson distribution. And we now added the fact that the frequency of one particular event in random samples of the two events, will follow the binomial distribution. An example was given from the death records of the Department of Health of the City of Bergen to illustrate this relationship.

If two sets of discs were randomly placed and mixed in a certain area, the hypothetical value for the mean variable free area around one of the sets was developed. This mean variable set 1 free area around the discs belonging to set 1 was thought to be independent of set 2. Each set would thus in a way act as if it were alone.

Models of two sets of randomly placed and randomly mixed discs were constructed. The mean variable free area observed on each of the models was compared to the hypothetical value. The observed mean variable free area tended to be somewhat lower than the hypothetical value. The difference between the observed and hypothetical values was not thought to be large enough to render our hypothesis unlikely.

The hypothesis for the relationship between mean variable free area and S. D. of division count also considered each

set of discs acting as if it were alone. This hypothesis was tested on our models of two sets of discs. In all cases the observed S. D. values were found to fall quite close to the values expected by our hypothesis, sometimes a trifle above, sometimes a trifle below.

The hypotheses developed for two sets of randomly placed and randomly mixed discs were then tested on reticulocytes in a smear.

It would not be sufficient to have the reticulocytes randomly mixed among the other erythrocytes. The reticulocytes and other erythrocytes would also have to be randomly placed. In order to obtain the most suitable reticulocyte smears, our own method was developed for preparing reticulocyte smears. The method was aiming at a maximum efficiency of staining combined with the most uniform distribution of erythrocytes.

In two reticulocyte smears from a person with hereditary spherocytosis and about 20 per cent reticulocytes, the mean diameter of reticulocytes as well as the mean diameter of total erythrocytes, was measured. The diameter of the reticulocytes was found to be some 4.5 per cent larger than the diameter of the total erythrocytes (which also included the reticulocytes).

The observed mean variable free area around the reticulocytes was found to agree well with the hypothetical value for two sets of randomly mixed discs.

The reticulocytes were counted in 60 equal divisions, and the observed S. D. of division counts was compared to the hypothetical value for two sets of discs. The observed S. D. of division counts was in 2 out of 3 instances slightly lower than the hypothetical value. An unconscious equalization of division counts might possibly explain this low observed S. D. of division counts.

## General conclusions

1 It was found theoretically that the mean free area of a random distribution of points was  $\frac{A}{n-1}$  where  $A$  was the total area and  $n$  was the number of points. For points more uniformly distributed, the mean free area would be larger than  $\frac{A}{n-1}$ . For distributions less uniform than a random distribution, the mean free area would be smaller than  $\frac{A}{n-1}$ .

2 Tests on 5 models of randomly distributed points on sheets of millimeter paper showed the observed values for mean free area to agree well with the theoretically calculated values ( $\frac{A}{n-1}$ ).

3 Observations on 5 models of randomly distributed points on sheets of millimeter paper showed the standard deviation of individual free areas to come very close to  $\frac{1}{n-1}$  ( $A$  still being the total area and  $n$  the number of points).

4 The mean variable free area around randomly placed discs was defined. The hypothesis was set forth that this mean variable free area was  $\frac{A}{n-1}$  minus 1.46

$D$  where  $A$  was total area,  $n$  was number of points and  $1.46 \times D$  was the room-

occupying structures enclosed within mean free area.

This hypothesis was tested on 11 models with varying disc density. The observed mean variable free areas were found to be scattered around the hypothetical value, sometimes a little above, sometimes a little below. The difference between observed and hypothetical value was in no case large enough to make our hypothesis unlikely.

5 When disc centers were counted in a number of equal divisions, the S. D. of an individual division count was calculated in usual manner. This S. D. was expressed as a fraction of the expected S. D. for a Poisson distribution with the same mean. The percentage deviation from the S. D. of a Poisson distribution was found to increase with increased size of the divisions. The reason for this was thought to be a neighbor-blocking effect of the discs in the border zone, most marked with small division sizes.

6 A hypothesis was set forth for a relationship between variable free area and S. D. of count in equal divisions. The hypothesis was

$$\frac{\text{S. D. divisions count} \times \text{discs}}{\text{S. D. division count} \times \text{points}} = \frac{\text{mean variable free area of } n \text{ discs}}{\text{mean free area of } n \text{ points}}$$

The hypothesis was thought to apply only to the S D of counts in really large divisions, with insignificant blocking effect of border zone discs.

Adapting factors were introduced in order to allow for the blocking effect of border zone discs, thus adapting our hypothesis to counts in smaller divisions.

Our hypothesis was tested on all 9 models of randomly placed discs. The observed values were found to be scattered around the hypothetical values, sometimes a little above sometimes a little below.

7 The formulae of Turner & Eadie and of Watanabe, were found to give an expected S D systematically larger than the observed values. Varying disc size superimposed random defects, and occasional overlapping were thought to result in a higher observed S D of individual division counts, and lower observed mean variable free area as compared to the values from our formula.

8. Reasons were given for measuring the erythrocyte diameter in dried preparations, with oil immersion system. Own investigations verified the fact that fixation and staining caused only insignificant change in diameter of erythrocytes.

9 The observed mean variable free area around erythrocytes was compared with the area expected according to our hypothesis for randomly distributed ideal discs. The observed mean variable free area tended to be slightly smaller than the hypothetical area. This was thought to fit well with the fact that the erythrocytes are not ideal discs with perfectly random distribution and no overlapping. Occasional overlapping and randomly placed defects in a smear will tend to make the observed mean variable free area somewhat smaller than our hypothetical value for ideal discs.

10. The observed S D of individual division count was calculated in different ways, and was compared with the S D expected according to our hypothesis for randomly distributed ideal discs. The observed S D tended to be slightly larger than the hypothetical value. This was thought to fit well with the fact that the erythrocytes are not ideal discs with perfectly random distribution and no overlapping. Occasional overlapping and randomly placed defects in a smear will tend to make the observed S D of individual division count somewhat larger than our hypothetical value for ideal discs.

11 When two sets of points are randomly distributed each set as well as the total of the two sets, will follow the Poisson distribution. And the frequencies of one particular set in random samples of the two sets, will follow the binomial distribution.

The mean free area around one set (e.g. set 1) that is the mean area free of

other set 1 points, will be  $\frac{A}{n_1 - 1}$ . The mean free area regardless of set will be  $\frac{A}{n_1 + n_2 - 1}$ .

12 Two sets of discs were assumed to be randomly mixed. If we therefore counted random samples of  $n$  discs regardless of set the frequencies of getting 0 1 2 ...  $n$  discs from set 1 was given by expansion of the binomial  $(p + q)^n$  where  $q$  was probability of set 1 and  $p$  the probability of set 2. With other words, we would have a Bernoulli distribution.

13. Two sets of randomly placed and randomly mixed discs were thought to behave as if each set were alone. That is, when  $n$  discs from set 1 were placed in area  $A$  the mean variable area free of other set 1 discs, was thought to be  $\frac{A}{n - 1}$  minus  $1.46 \times D$ .

14 The hypothesis previously set forth for relationship between variable free area and S. D. of count in equal divisions, was expected to be valid also for each one of two randomly mixed sets of discs. This would again imply that the discs would behave as if each set were alone. The hypothesis was

$$\frac{\text{S. D. division count } 1 \text{ disc}}{\text{S. D. division count } n1 \text{ points}} = \frac{\text{mean var free area of } n1 \text{ discs}}{\text{mean free area of } n1 \text{ points}}$$

Adapting factors made the hypothesis useful for counts in smaller divisions.

This hypothesis was tested on 5 models containing two sets of randomly placed and randomly mixed discs. The observed values were in all cases found to fall quite close to the values expected by our hypothesis, sometimes a trifle above, sometimes a trifle below.

15 Our own method of preparing a reticulocyte smear was developed aiming at a maximum efficiency of staining combined with the most uniform distribution of erythrocytes.

16 The observed mean variable free area around reticulocytes was compared with the area expected according to our hypothesis for two sets of randomly placed and randomly mixed ideal discs. The observed mean variable free area came close to the hypothetical area.

17 The observed S. D. of individual reticulocyte division counts, was compared with the S. D. expected according to our hypothesis for two sets of randomly placed and randomly mixed discs. The observed S. D. was in 2 out of 5 instances slightly smaller than the hypothetical S. D. This smaller observed S. D. might possibly be due to unconscious equalization during counting. The fact that the observed mean variable free area agreed so well with the hypothetical value, was thought to substantiate this explanation.

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(The abbreviations employed are those adopted by World Medical Periodicals, 3rd ed., 1961)

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Fig 16. PJS I The first photograph of sample with the 50th lowest index of dispersion. Photographed with oil immersion March 2.

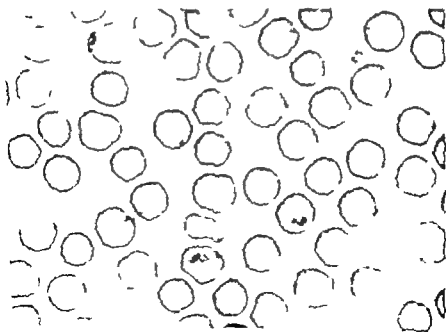


Fig 17. PJS I The first photograph of sample with the 50th lowest index of dispersion. Photographed with oil immersion June 5.

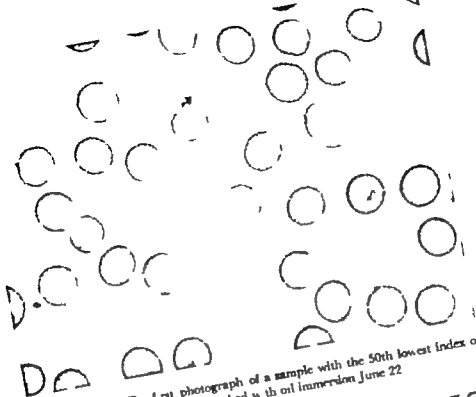


Fig 18. J H II The first photograph of a sample with the 50th lowest index of dispersion. Photographed with oil immersion June 22

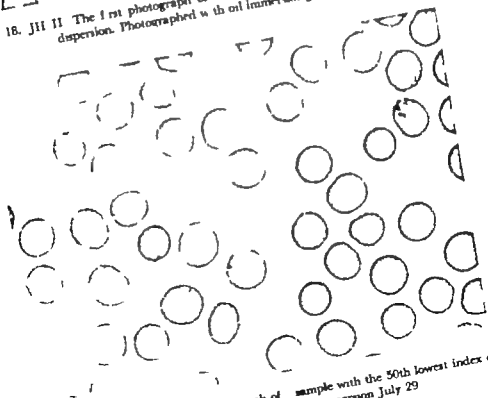


Fig 19 J H III The first photograph of a sample with the 50th lowest index of dispersion. Photographed with oil immersion July 29

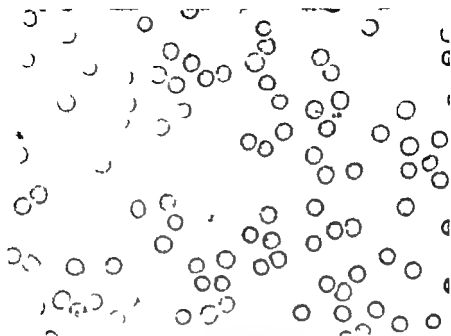


Fig. 20 J H. IV The photograph in which the difference in count between left upper and right lower division has the 50th lowest value. Photographed with dry lens objective August 24

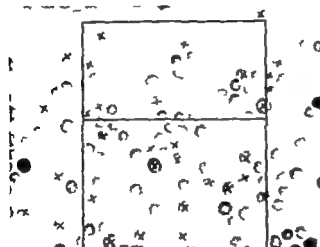
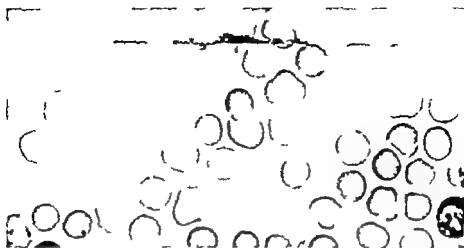
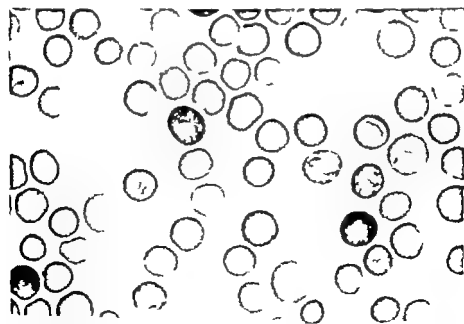


Fig 21

A. M. V Reticulocyte smear photographed with oil immersion and dry lens objective. Reticulocytes on dry lens photograph marked during microscopy







# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 410

## PULMONARY BLOOD VOLUME IN MAN

*A Study Using the Double Indicator  
Technique in Patients with Cardiovascular Disease*

BY

SVEN ÅKE FORSBERG

*Accompanies Vol. 175*

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GÖTEBORG 1964



# ACTA MEDICA SCANDINAVICA

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# PULMONARY BLOOD VOLUME IN MAN

*A Study Using the Double Indicator  
Technique in Patients with Cardiovascular Disease*

BY

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GÖTEBORG 1964

Translated  
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# ABBREVIATIONS

Key to abbreviations used in Tables 10 to 11 will be found on page 75

|                          |  |
|--------------------------|--|
| <i>Art</i>               | = Systemic artery  |
| $(a-v)O_2$               | = Average arteriovenous oxygen difference                                      |
| <i>BSP</i>               | = Bromsulphalein   |
| <i>BTPS</i>              | = Body temperature and pressure saturated                                      |
| <i>CBV</i>               | = Central blood volume   |
| <i>CG</i>                | = Cardilogreen   |
| <i>CO</i>                | = Cardiac output   |
| <i>CO<sub>BSP</sub></i>  | = CO determined with <i>BSP</i>  |
| <i>CO<sub>CG</sub></i>   | = CO determined with <i>CG</i>   |
| <i>CO<sub>ave</sub></i>  | = Average of <i>CO<sub>BSP</sub></i> and <i>CO<sub>CG</sub></i>                |
| <i>CO<sub>LA</sub></i>   | = CO determined by <i>BSP</i> or <i>CG</i> injection into the left atrium      |
| <i>CO<sub>PA</sub></i>   | = CO determined by <i>BSP</i> or <i>CG</i> injection into the pulmonary artery |
| <i>CO<sub>Fick</sub></i> | = CO determined by Fick's method   |
| <i>H</i>                 | = Hematocrit   |
| <i>HR</i>                | = Heart rate   |
| <i>LA</i>                | = Left atrium  |
| <i>MTT</i>               | = Mean transit time  |
| <i>P<sub>A</sub></i>     | = Mean pressure in a systemic artery   |

|                       |   |
|-----------------------|---|
| <i>P<sub>LA</sub></i> | = Mean pressure in the left atrium      |
| <i>P<sub>PA</sub></i> | = Mean pressure in the pulmonary artery |
| <i>PA</i>             | = Pulmonary artery                      |
| <i>PBV</i>            | = Pulmonary blood volume                |
| <i>PVR</i>            | = Pulmonary vascular resistance         |
| <i>STPD</i>           | = Standard temperature and pressure dry |
| <i>SV</i>             | = Stroke volume                         |
| <i>TBF</i>            | = Total blood volume                    |
| $\dot{V}_E$           | = Total ventilation                     |
| $\dot{V}_{O_2}$       | = Oxygen consumption                    |

## Statistical Symbols

|                       |   |
|-----------------------|---|
| <i>b</i>              | = Coefficient of regression                         |
| <i>b<sub>yx</sub></i> | = Coefficient of regression of <i>y</i> on <i>x</i> |
| <i>d</i>              | = Difference  |
| <i>r</i>              | = Coefficient of correlation                        |
| <i>S</i>              | = Standard deviation                                |
| <i>S<sub>b</sub></i>  | = Standard deviation of regression coefficient      |
| <i>S<sub>d</sub></i>  | = Standard deviation of difference                  |
| <i>S<sub>2</sub></i>  | = Standard deviation of mean difference             |
| <i>S<sub>r</sub></i>  | = Standard deviation of correlation coefficient     |
| <i>S</i>              | = Residual standard deviation in <i>y</i>           |



## INTRODUCTION

An assessment of haemodynamic conditions in the lungs requires adequate information on the pressure flow and volume of the blood in the pulmonary circulation. Our present knowledge of the pressure and flow of blood in the human pulmonary circulation under normal and abnormal conditions is reasonably complete largely thanks to the important and substantially unanimous experiences amassed following FORSEMAN's and COURNAND's pioneering researches. But there is still no consensus of opinion regarding the magnitude of the pulmonary blood volume in man (6 51 77 99 111); our knowledge is fragmentary and various methods purported to measure it have often yielded discrepant results. Hence additional attempts to estimate the pulmonary blood volume seem justified not least because information on its changes under various physiological and abnormal conditions or in response to drugs probably would help us to understand the mechanisms for active and passive regulation of the pulmonary vascular bed (99).

Provided the rate of blood flow is constant the volume of blood entering the lungs through the pulmonary artery is equal to that leaving them at the entry of the pulmonary veins into the left atrium. One might call the capacity of the vascular bed between these two points the "total pulmonary blood volume". At

present the bronchial circulation may be disregarded because its interchange of blood with the pulmonary circulation is negligible except in some markedly abnormal conditions (15 22 39 40 47 81).

Theoretically the total blood volume in an organ may be divided into a circulating portion and a comparatively stagnant portion (113). The boundary between them is inexact and depends upon how one defines a negligible flow. In view of the structure and function of the vascular system it is reasonable to assume that all organs contain vascular pathways with very slow flow rates. But whether more or less stagnant blood constitutes an appreciable proportion of an organ's total blood volume is another matter. GRIMBY *et al* (50) were unable to demonstrate the presence of stagnant blood pools in the lungs of dogs, and there is no evidence suggesting that the human vascular system incorporates any such pools (32 65, 97 98).

Various methods have been adopted in attempts to estimate sudden changes in total pulmonary blood volume. Spirometric alterations accompanying say postural changes or provoked blood trapping in the limbs have been adduced to reflect changes in total pulmonary blood volume (56 111). Using a combination of spirometry plethysmography lung capacity measurement and cardiac volume



estimation, SJÖSTRAND (123 1°4) obtained an indirect measure of pulmonary blood volume changes. And extrathoracic measurement of the radioactivity of an indicator homogeneously mixed with the blood has been employed for studying rapid fluctuations of the pulmonary blood volume (10 83 143). The absolute magnitude of the pulmonary blood volume has been measured *post mortem* in animals (82, 107) and man (4).

The circulating pulmonary blood volume can be determined with the aid of an indicator dilution technique. The exhaustive investigations into the theoretical basis for blood flow estimation by indicator techniques were surveyed by ZIEGLER (140 14). Over the years around 1830 HAMILTON *et al* (65 73 92) laid down the principles for determination of blood flow and circulating blood volume and their concepts have remarkably withstood the test of time. At an early stage HAMILTON and his collaborators (55 73) demonstrated in flow models and perfused heart-lung preparations that the indicator technique in specified circumstances really does measure true blood flow. This has been verified (13 20 88 110 120) and the technique compared with Fick's direct method, a generally accepted procedure for blood flow estimations *in vivo*. The theoretical basis for the application of Fick's method and its sources of error have been debated (19 47 1°9 137). SZILLY, VERLICH & GRIGOR (117) reported close agreement between the Fick method and direct flow determinations in animal experiments. The results of experimental applications of Fick's technique and comparisons between it and indicator dilution methods now compose a profuse and

tangled literature which in recent years has been analyzed in survey papers (3 28 54 63 138). Today it is universally accepted that Hamilton's indicator dilution technique correctly measures the intravital blood flow provided specified procedural and haemodynamic conditions are satisfied. Summaries comparing the results of Fick's technique and the indicator dilution method (28 34, 35 63 126 138) disclose that whereas there is little or no systematic difference between them they may exhibit considerable discrepancies in individual cases. Owing to their dissimilar characters these two methods can never measure blood flow during concurrent periods of time.

The validity of circulating blood volume measurements by Hamilton's technique has been evaluated theoretically (63 146 147). It has also been demonstrated experimentally by flow models (13 20 55) and in perfused heart-lung preparations (120). In experiments on dogs *in vivo* SCHLAXT *et al* (118) found that the circulating cardiopulmonary blood volume was strongly correlated with, and did not deviate systematically from the corresponding volume of blood extracted from the excised organs immediately after ligation of their afferent and efferent vessels.

Several workers have attempted to use the indicator dilution technique for estimating the pulmonary blood volume by injecting the indicator into the pulmonary artery or farther upstream. LAGERLÖF *et al* (76) determined the pulmonary blood volume in man by subtracting from the measured central blood volume a fraction corresponding to its estimated extrapulmonary portions. NEWMAN *et al* (85)

used the slope of the dilution curve and the cardiac output for calculating pulmonary blood volume. However it has been shown that this "Newman volume" does not measure the pulmonary blood volume and lacks definite anatomical and physiological equivalents (3, 30, 53, 55, 87, 140, 146). RABINOWITZ & RAPAPORT (109) adopted Bradley's indicator equilibration method for calculating the pulmonary blood volume. However it is important to realize the fallacy of discussing the results of Bradley's method in terms of pulmonary blood volume. Theoretically it measures the central blood volume from the pulmonary artery to arteries equidistant with the blood collection point in a systemic artery and the pulmonary blood volume constitutes merely a part of this volume. And, unlike RAPAPORT *et al.* (110) BRAUFWALD *et al.* (13) deemed this method unsuitable for determination of the blood volume in central vascular segments. Other workers have sought to determine the circulating pulmonary blood volume by extrathoracic measurement of the radioactivity of an injected indicator. A survey of this method — also called quantitative radiocardiography — and experimental analyses have been published by DONATO and his group (\*6, \*7, 51, 80). As applied by LAMMERANT (77) and others (17, 23, 91, 106), the radiocardiographic method includes in the pulmonary blood volume an ill-defined blood fraction in the right and left sides of the heart (51, 80).

With refinements of the technique for catheterization of the left atrium (114) it became feasible to apply Hamilton's method directly to determination of the circulating pulmonary blood volume in man in terms of the difference between

the blood volume circulating from the pulmonary artery to a systemic artery and that circulating from the left atrium to the same systemic artery. The use of this double indicator method was initially applied by KUNIDA in 1933 (75) who a short interval after injecting an indicator into the pulmonary artery injected the same indicator into the left atrium. The same technique was later adopted by MILNOR, JOSE & MCGAFF (80), FERNANDEZ ARMENDIA & TAQUINI (39), OAKLEY *et al.* (90) and MCGAFF *et al.* (80). DOCK *et al.* (25) and VARNATSKAS *et al.* (123) are so far alone in injecting simultaneously two different indicators. Experimentally induced changes in circulating pulmonary blood volume in man have been reported from some of those laboratories using the double indicator technique (55, 66, 99, 104, 116, 132, 145). Owing to the arduous examination, all series published hitherto have been composed of patients subjected to diagnostic heart catheterization. Results derived from such heterogeneous series are difficult to assess.

Unless otherwise stated, the term pulmonary blood volume (abbreviated *PBV*) will hereinafter be used synonymously with circulating pulmonary blood volume determined in accordance with Hamilton's principles with the aid of the double indicator technique.

The present investigation was designed to elucidate the experimental premises for *PBV* determination in man by the double indicator technique to assess the method's reproducibility in duplicate determinations at rest, a necessity for analysis of *PBV* changes in response to altered physiological or pharmacological conditions,

and to analyze the magnitude of *PBV* and its relations to other clinical and physiological factors of rest

The method for *PBV* determination was analyzed on the basis of observations made in three groups of patients. In one group, known as the new series *PBV* was measured, in another *PBV* was not measured but the two indicators were compared by being injected simultaneously via the same catheter and in the

third group called the "old series" *PBV* was also measured, although the principles underlying one of the dye dilution methods deviated somewhat from those in the two other series. Considering that this difference did not systematically affect the results, the "old series" and the "new series" were regarded as equivalent for the subsequent analysis of the magnitude of the pulmonary blood volume and of its interrelations with other factors

## CHAPTER 2

### CLINICAL MATERIAL

#### DIAGNOSTIC PRINCIPLES

The cardiovascular diagnoses of the patients included in the present study are based on available and applicable methods: the main ones include physical examination of the heart, phonocardiography, ECG with chest leads, roentgenological examination of the heart and lungs in various projections with cardiac volume estimation, deductions drawn from heart catheterization, and selective angiocardiology. Angiocardiology was usually dispensed with in the presence of distinct clinical indications of mitral stenosis. The functional diagnoses are based on a careful clinical history comprising classification into functional groups according to the recommendations of the New York Heart Association (24). Among the diagnoses specified in the tables, those in parentheses were deemed to have slight haemodynamic significance.

#### OLD SERIES

The old series consisted of 34 patients selected from subjects scheduled for heart catheterization for diagnosed or suspected cardiovascular disease. The diagnoses to-

gether with clinical and laboratory findings are specified in Table 10, page 75 (Patients 1-34). Patients 1-32 are identical with those presented by VARNHAUS *et al.* in 1963 (133). When the calculations in this paper were checked, it turned out that the mean transit time in three patients was slightly wrong.<sup>1</sup> The diagnosis of mitral stenosis in Patients 12, 23 and 31 has been supplemented with chronic obstructive pulmonary disease, a major feature of the clinical picture. Here the ages of the patients in the old and the new series are specified in terms of the integral number of years from the day of birth to the day of the examination and this system has changed some of the ages in the former publication by at most 1 year.

The age and sex distribution of the patients in the old series will be found in Table 1. The ages ranged from 17 to 63 and averaged 43 years.

---

<sup>1</sup> The corrections caused the pulmonary blood volume to be changed to 510 ml (-5 ml) in Patient 1, to 511 ml (+3 ml) in Patient 3 and to 670 ml (-73 ml) in Patient 8. In addition  $PBI/m BSA$  became 340 ml (-4 ml) in Patient 13. None of these corrections affect any of the results published previously, but whenever any of them are considered in the present monograph the corrected values are used.

Table 1. Age and sex distribution of the old series.

| Age group | Men | Women | Total |
|-----------|-----|-------|-------|
| 13-19     | 1   | 0     | 1     |
| 20-24     | 4   | 0     | 4     |
| 25-29     | 1   | 0     | 1     |
| 30-34     | 2   | 1     | 3     |
| 35-39     | 2   | 1     | 3     |
| 40-44     | 2   | 4     | 6     |
| 45-49     | 1   | 4     | 5     |
| 50-54     | 3   | 2     | 5     |
| 55-59     | 1   | 4     | 5     |
| 60-64     | 0   | 1     | 1     |
| Total     | 17  | 17    | 34    |

The clinically dominant cardiovascular diagnoses were

|  | of pat |
|--|--------|
| Mitral valvular disease                                | 11     |
| Mitral valvular disease with systemic hypertension     |        |
| Combined mitral and aortic valvular disease            | 5      |
| Combined mitral, aortic and tricuspid valvular disease | 1      |
| Aortic valvular disease                                | 7      |
| Aortic coarctation                                     | 3      |
| Coronary heart disease with systemic hypertension      | 1      |
| Constrictive pericarditis                              | 1      |
| Cardiomyopathy   | 1      |
| Cardiovascular abnormality                             | 2      |

Three patients exhibited signs of chronic obstructive pulmonary disease in two of them associated with mitral stenosis and in one associated with mitral stenosis and aortic valvular disease.

At the pulmonary blood volume determination at rest the peak systemic arterial blood pressure exceeded 100 mm Hg during systole or 100 mm Hg during diastole

in 9 patients (Nos 5 7 9 10 19 23 27 28 32). Patients 27 and 32 had aortic coarctation and the specified pressures were registered in the brachial artery in the high pressure system above the coarctation. In three of the remaining seven patients (Nos 5 9 10) chronic systemic hypertension was judged a significant component of the clinical picture.

Patient 17—with a diagnosis of cardiomyopathy—already had sustained the cardiac lesion during childhood, possibly as a sequel to diphtheria. All chambers of the heart were explored with catheters in connection with the pulmonary blood volume determination. It was found that the elevated pressure in the left atrium was associated with a raised end-diastolic pressure in the left ventricle and angiocardiology disclosed dilatation of the left ventricle as well as of the left atrium.

At the pulmonary blood volume determination 22 patients had sinus rhythm 11 had auricular fibrillation and 1 had auricular flutter. 20 of the 34 patients were on digitalis.

Classification by functional groups revealed that 7 patients were in Group I 10 in Group II, 11 in Group III and 6 in Group IV.

## NEW SERIES

The new series comprised 38 patients selected in accordance with the same principle as those in the old series. Their age ranged from 17 to 60 and averaged 42 years. The patients' sex and age distribution is set out in Table 2, the diagnoses and relevant data from the examinations are presented in Table 11 page 75.

Table ... Age and sex distribution of the new series.

| Age group | Men | Women | Total |
|-----------|-----|-------|-------|
| 15-19     | 1   | 1     | 2     |
| 20-4      | 1   | 1     | 2     |
| 25-40     |     |       | 4     |
| 30-34     | 1   | 1     | 2     |
| 35-39     | 1   | 0     | 0     |
| 40-44     | 2   | 5     | 5     |
| 45-49     | 5   | 5     | 10    |
| 50-54     | 5   | 2     | 8     |
| 55-59     | 1   | 0     | 1     |
| 60-64     | 1   | 0     | 1     |
| Total     | 1   | 1     | 39    |

The clinically dominant cardiovascular affections were:

|   | No. of pat. |
|---|-------------|
| Mitral valvular disease                               | 12          |
| Mitral a. valvular disease with systemic hypertension | 1           |
| Combined mitral and aortic valvular disease           | 4           |
| Aortic valvular disease                               | 4           |
| Pulmonary stenosis                                    | 1           |
| Subaortic stenosis                                    | 2           |
| Aortic coarctation                                    |             |
| Left trial myxoma                                     |             |
| Cardiomyopathy  | 3           |
| Paroxysmal tachycardia                                | 1           |

Among the 28 patients with valvular disease No. 39 with pulmonary stenosis and Nos. 56 and 58 with aortic stenosis were deemed to have congenital affections. 1 others had a history of rheumatic fever or chorea with or without carditis. Though the history was negative in the last 5 the type of valvular disorder and occasionally observations made at a subsequent cardiac operation suggested that the aetiology was rheumatic in these cases too.

At the pulmonary blood volume determination peak systemic arterial pressures exceeding 160 mm Hg during systole and 100 mm Hg during diastole were recorded in 10 patients (Nos. 25, 26, 37, 39, 41, 45, 49, 50, 63, 72). Two of them (Nos. 50 and 72) had aortic coarctation and the systemic arterial pressures specified for them were registered in the brachial artery in the high pressure system above the coarctation. In one of the remaining 8 patients (No. 37) chronic systemic hypertension was considered a significant feature of the clinical picture.

The cardiomyopathies diagnosed in Patients 4, 6, and 70 call for some comment. At the time of the pulmonary blood volume determination Patient 4 was symptomless but the ECG was abnormal and the heart considerably enlarged with left atrial and ventricular dilatation. The chest X ray disclosed congestion of the pulmonary vessels and minor densities bilaterally in the parenchyma. Chronic unspecific inflammation with fibrosis was demonstrated in the supraclavicular lymph nodes. Seven years ago there had been a period of fever, generalized lymph node enlargement, anaemia and splenomegaly. A few months before the pulmonary blood volume determination the patient again had fever and exhibited signs of cardiac disease. A thorough clinical assessment notwithstanding the best diagnosis that could be made was chronic systemic disease with cardiac involvement.

About a year before the pulmonary blood volume determination, Patient 6 had a sudden onset of presumed acute myocarditis with high temperature and cardiac decompensation. As symptoms and signs of a grave cardiac lesion per-

ated, the patient was given  $^{131}\text{I}$  in order to subdue thyroid function. At the time of the pulmonary blood volume determination he was on a small substitution dose of thyroid extract but showed clinical evidence of hypothyroidism. Whereas clinical examinations disclosed mild mitral stenosis the outstanding finding was pronounced left ventricular dilatation — an indication confirming myocardial affection.

For about a year and a half before the pulmonary blood volume determination Patient 70 had been undergoing treatment in hospital for symptoms of fatigue and uncharacteristic recurrent pains in the chest with mild fever hypercholesterol aemia and in the ECG inverted T waves. Later the symptoms and signs were chest pains, breathlessness, palpitations and paroxysmal tachycardia. Thorough examinations including left atrial and coronary angiocardiology at the time of the pulmonary blood volume determination re-

vealed no persistent abnormalities other than an abnormal ECG and hypercholesterolaemia.

Patient 61 had funnel chest of moderate degree. It was not deemed clinically significant. Since his childhood Patient 70 had tended to develop asthmatic bronchitis following upper respiratory tract infections. At the time of the pulmonary blood volume determination he was symptomless and physical examination disclosed no signs of obstruction of the upper respiratory tract nor of emphysema. The X ray appearance of his lungs was normal.

At the time of the pulmonary blood volume determination 23 patients had sinus rhythm, 14 had auricular fibrillation and 1 had complete auriculoventricular block. 28 of the 33 patients were on digitalis.

Classification by functional groups revealed that 3 patients were in Group I, 25 in Group II, 10 in Group III and none in Group IV.

## CHAPTER 3

### METHODS

#### EXAMINATION PROCEDURE

The patients were examined in the supine position, fasting, without premedication. A short-acting barbiturate might have been given the preceding evening. The catheters were inserted under local anaesthesia (5% Carbocain, AB Bofors). When pressure measurements required for routine diagnosis had been made the catheters were placed in position—one in the pulmonary artery another in the left atrium and the third either in the distal aorta or in the brachial artery. Heparinized physiological saline (8000 I.U. per litre) was infused slowly into the catheters in the pulmonary artery and left atrium and the arterial catheter was flushed intermittently with the same fluid.

The various steps in the complete procedure for pulmonary blood volume determination were carried out in the order shown below after the patient had rested for about 20 minutes while no catheter manoeuvres took place.

- 1 Expired-air collection commenced.
- 2, 3—4 minutes later one ECG lead was recorded and the pressures measured in the pulmonary artery, left atrium and a systemic artery.
- 3 While an ECG was recorded blood samples were taken for estimation of the arteriovenous oxygen difference.

- 4 An arterial blood sample was drawn for haematocrit determination.
- 5 During ECG recording the indicator dilution procedure was done by simultaneously injecting 5 ml of one of the indicators (bromsulphalein and cardio-green) into the pulmonary artery and 5 ml of the other indicator into the left atrium, followed by fractionated collection of blood from a systemic artery.
- 6 An ECG was recorded and blood pressures were measured once more.
- 7 Expired-air collection was discontinued.

Expired air was not always collected and very occasionally oxygen saturation was not estimated.

At least 20 minutes lapsed before any *PBF* determination was repeated. One determination took 6 to 8 minutes and was attended by a total blood loss of 75 to 90 ml, the amount of physiological saline administered before each procedure being of the same order.

#### CATHETERIZATION

The following catheter types were used for insertion into the vessels specified.



- (i) Pulmonary artery: a Courmand catheter (U.S.C.I. No 8) with a length of 102 cm and a capacity of  $3.1 \text{ cm}^3$  1 cm from the closed tip 4 holes in the wall are equispaced around the perimeter
- (ii) Left atrium: a thin walled Ödman-Ledin catheter (Kila AB Sweden) with a length of 71 cm and a capacity of about  $1.9 \text{ cm}^3$  1 cm from the open tip there is 1 hole in the wall.
- (iii) Aorta: a catheter similar to (ii) but having a length of 85 cm and a capacity of approximately  $2 \text{ cm}^3$
- (iv) Brachial artery: a polyethylene catheter No 203 with a length of 40 cm and a capacity of some  $0.6 \text{ cm}^3$

The catheter was guided into the stem of the pulmonary artery via an exposed cubital vein whereupon the catheter was affixed near its point of entry into the arm. This arm was not moved subsequently. Transseptal puncture of the left atrium was done by the percutaneous route via the right femoral vein, as described by PAULIN & VARNAUKLAS (1955). On the arterial side a catheter was inserted percutaneously either into the brachial artery or via the femoral artery into the distal aorta. All catheters except that in the brachial artery were manoeuvred under fluoroscopic control.

## BLOOD PRESSURES AND HEART RATES

The pulmonary arterial, left atrial and systemic arterial blood pressures were measured simultaneously by connecting each of the three catheters to its own

electromanometer set composed of a pressure transducer of variable inductance type (EMT 490A, Elema-Schönander AB) feeding an amplifier (EMT 485 Elema-Schönander AB). The pressures and one ECG lead were registered photographically with the aid of a multichannel recorder (Electrocardiograph, Type EM 130 Elema-Schönander AB).

All pressures are given in mm Hg referred to ambient pressure a frontal plane 5 cm dorsal to the sternal angle being taken as zero level. The pressure transducers to the catheters in the pulmonary artery and left atrium had a common physiological saline reference pressure system and the catheter in a systemic artery a separate mercury reference system. Mean pressure variations were obtained by electrical integration (amplifier time constant = 0.8 secs) and low paper speed (1 cm per sec) rapid fluctuations by using high paper speed (4 cm per sec) and minimal electrical damping. Each registration included reference pressures at the beginning and at the end. Systolic diastolic and mean pressure levels were estimated by manually smoothing the curves for at least two respiratory cycles. With one exception the pressures specified for patients in the new series are the average of readings taken before and after the indicator dilution procedure while those for the old series sometimes were registered either before or after this procedure.

The linearity of each complete system of pressure transducer amplifier and recording channel was checked by recording series of known calibration pressures and measuring the corresponding deflections registered on the paper. When the catheters to the pulmonary artery and left

atrium both were passed into the right atrium as was done in 97 of the 38 patients in the new series the differential pressure was as high as 1 mm in - patients and less than 1 mm in the others.

Heart rates were determined from the R deflections in the ECG corresponding to 10 strokes of the heart during the undamped blood pressure measurements and to 20 strokes during the indicator dilution procedure. The latter figures are given in the tables.

## VENTILATION AND OXYGEN CONSUMPTION

The expired air to be analyzed was collected in a Douglas bag immediately after it had been scavenged with the patient's expired air and evacuated. After collection the bag was emptied with a suction pump through a gas flow meter (Eschweiler & Co). While the bag was being emptied a pause was made during which a small gas receiver was filled with air from the bag which was analyzed in a Scholander gas analysis apparatus (Eschweiler & Co). Duplicate determinations were invariably made. Ventilation (*BTPS*) and oxygen consumption (*STPD*) were calculated.

## OXYGEN SATURATION

A blood sample was drawn with a Luer Lok II glass syringe moistened with heparin and containing a drop of mercury in the dead space. The analysis was carried out immediately by a modification of NAHAS spectrophotometric method (94) as described by HOLMGRÉN & PERSSON (60). The isobest point was found to be

503 mμ. The extinctions were read in a Beckman B spectrophotometer.

## OXYGEN CAPACITY

This analysis was done on the same blood sample as was used for determination of the oxygen saturation of arterial blood, using a spectrophotometric procedure according to DEARBORN & AUSTIN (30) with potassium cyanide and potassium ferriyanide and reading the extinction at 540 mμ. in a Beckman B spectrophotometer. The calculations were based on the means of duplicate determinations.

## HEMATOCRIT

An arterial blood sample was drawn into an Ellermann tube. After thorough mixing two 50 mm hematocrit capillary tubes were filled and centrifuged at 6000 rpm for 15 minutes. The centre of the centrifuge axis was 9 cm from the far end of the tubes where the centrifugal force attained some 3600 g. The means of duplicate determinations were used for calculating the hematocrit values which were not corrected for trapped plasma.

## INDICATOR PROCEDURES

Blood was collected in 40 heparinized Ellermann tubes for one second per tube using a synchronous motor driving a collection wheel. Irrespective of whether blood was collected from the brachial artery or from the distal aorta the flow was of the same order and varied from one patient to another between approximately 1.5 and 1.8 ml/sec.

Concentrations of the indicators were analyzed in a Beckman B spectrophotometer

**Bromsulphalein (BSP)** *BSP* concentrations were determined at a wavelength of 580  $m\mu$ . The cuvette was filled with 3.0 ml of an alkaline buffer solution<sup>1</sup> from a tared automatic pipette. After addition of 0.1 ml or if required, 0.05 ml of the sample, the extinction was read. Then 0.1 ml of an acidifying solution<sup>2</sup> was added, any *BSP* present thereby being decoloured. The extinction was determined anew and subtracted from the former extinction value. The alkaline buffer solution was employed as a blank.

A 5 per cent solution in ampoules from a large manufacturing lot was used for injection of 5 ml, which was always made with the same syringe. Its content of *BSP* expressed in extinction units was redetermined for every new *BSP* consignment in several dilutions with physiological saline to 500 ml.

The indicator was injected by hand with a syringe having a stop on the plunger shaft ensuring that always the same indicator volume was injected. 3 to 4 seconds after the end of the injection the plunger was quickly retracted, thereby removing any residual indicator in the

catheter together with a few ml of blood. It was assumed that at the time of retraction the indicator injected into the patient had disappeared from the point of injection and not reappeared by recirculation. The indicator residue was diluted with physiological saline to 500 ml and the extinction was read in the supernatant after centrifugation of a sample of this dilution.

The quantity of *BSP* injected into the patient (*E*) was calculated as the difference between the *BSP* content in the syringe and the indicator residue expressed as the extinction value for a dilution to 1 litre.

**Cardiogreen (CG)** *CG* concentrations were read at wavelength 806  $m\mu$ . The sample was diluted as for *BSP* analysis and the extinction determined after acidification. The blank was a mixture of 3.0 ml of alkaline buffer solution and 0.1 ml of acidifying solution.

From *CG* powder (HYGSOX WESTCOTT & DUNNING Inc) a 0.3 per cent aqueous stock solution was freshly prepared for each patient. The same syringe was always used for injection of 5 ml *CG*. Its content of *CG* expressed in extinction units was determined for every stock solution prepared by means of dilutions with blood bank plasma. 1 ml of the *CG* stock solution was drawn up in a precision pipette and was diluted with blood bank plasma to 100 ml. The extinction was read and the extinction value of a sample of *CG* free blood bank plasma subtracted. This determination was consistently duplicated and the averaged result used in the calculations. The ratio of the volume of the pipette to that of the syringe (injected

<sup>1</sup>

|  |           |
|--|-----------|
| Dibasic sodium phosphate<br>( $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ )      | 24.40 g   |
| Trisbasic sodium phosphate<br>( $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$ )    | 3.54 g    |
| Sodium toluene-p-sulphonate<br>( $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{Na}$ ) | 6.40 g    |
| Distilled water  | t 1000 ml |

<sup>2</sup>

|  |          |
|--|----------|
| Monobasic sodium phosphate<br>( $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ ) | 69 g     |
| Distilled water  | t 250 ml |

volume) had been found with the aid of an analytical balance (Mettler, type B5). The CG content of the syringe was calculated from this ratio

The CG injection and retraction was made as for BSP. The indicator residue withdrawn was diluted to 100 ml with blood bank plasma and analyzed in the supernatant after centrifugation of a sample of this dilution. The extinction value of the CG free blood bank plasma was subtracted

The quantity of CG injected into the patient ( $E_i$ ) was calculated as for BSP

The extinction values of BSP and CG ( $E_{pi}$ ) were read in undiluted plasma from each tube from the blood collection wheel. For both indicators a semilogarithmic dilution curve was constructed by extrapolation from the rectilinear portion of the descending arm of the curve to the zero level expressed as the mean of the small extinctions in a preliminary sample and in the tubes before the commencement of the extinction curve.

## CARDIAC OUTPUT

Cardiac output according to the indicator dilution method was derived from the expression (63):

$$CO \text{ (l/min)} = 60 \frac{E_i}{TEE_{pi}} \frac{100}{100-H}$$

where

$E$  = The indicator quantity injected into the patient expressed as the extinction value for dilution to one litre

$T$  = The blood collection time in second for each specimen (tube)

$TEE_{pi}$  = The area of the extrapolated indicator curve with indicator concentration ( $E_{pi}$ ) expressed in extinction units

$H$  = Hematocrit in per cent.

Cardiac output was calculated according to Fick's direct method with the formula.

$$CO \text{ (l/min)} = \frac{\dot{V}_{O_2}}{(a-t)_{O_2}}$$

where  $\dot{V}_{O_2}$  = Oxygen consumption (ml/min STPD) and  $(a-t)_{O_2}$  = average arteriovenous oxygen difference (ml/l STPD).

## CIRCULATING PULMONARY BLOOD VOLUME (PBV)

PBV was calculated from the expression

$$PBV \text{ (ml)} = \frac{MTT_{pulm} \text{ (secs.) } CO \text{ (l/min)} 1000}{60}$$

Cardiac output (CO) was calculated in terms of the average of the simultaneous determinations with BSP and CG except on 5 occasions when one of the injections was attended by slight leakage which, however did not interfere with computation of mean transit time (MTT). The site of the indicator injection was varied at random from one patient to another but was kept constant for repeated trials on the same patient.

The mean transit time through the lungs ( $MTT_{pulm}$ ) was calculated as the difference between the mean transit times from pulmonary artery to the blood collector and to the latter from the left atrium,

ATT for each indicator being found from the formula (55)

$$ATT = \frac{\Sigma(C \cdot T)}{\Sigma C}$$

BSP and CG were injected with syringes of the same type containing similar volumes (5 ml) through catheters of approximately equal volumes (1.9 ml  $\pm$  1 ml) simultaneously by hand by the same person at the same time as blood collection was commenced by an assistant. The injection time in model experiments was about 0.8 seconds.

### PULMONARY VASCULAR RESISTANCE (PVR)

PVR is expressed in units representing the ratio of fall in pulmonary vascular pressure to cardiac output thus.

$$PVR = \frac{P_{PA} - P_{LA} \text{ (mm Hg)}}{CO \text{ (l/min)}}$$

In these computations the same cardiac output values were used as for determination of pulmonary blood volume.

### BODY SURFACE AREA (BSA)

The patient was weighed to the nearest 0.1 kg. On the same occasion his stature was measured. The body surface area was obtained by entering a DuBois nomogram.

### CARDIAC VOLUME

With two exceptions in the new series cardiac volume was measured roentgenologically with the patient lying down in

accordance with the method described by LARSSON and KJELLBERG (78) and modified by KJELLBERG and coworkers (73 a, 73 b). The exposure was not triggered by the ECG complex; the frontal projection was exposed with the roentgen tube angled 30° in cranial direction from a transversal plane through the patient's heart. The constant 0.53 was consistently used in the formula for cardiac volume.

In the entire old series and Patients 35 and 54 from the new series the cardiac volume was estimated in standing patients according to the method published by JOXELL (77) with a focus-to-film distance of 160 cm and the constant 0.4 in the expression for cardiac volume.

### COMMENT ON METHOD AND PROCEDURE IN OLD SERIES

Since appropriate methods and procedures were evolved over a comparatively long period of time it was unavoidable that the old series and the new series were not treated exactly alike. Points of difference will be considered in the following.

Cardiogreen concentrations were read at 780 m $\mu$ . After dilution with an aqueous plasma solution the indicator content of the special CG syringe was estimated for each of several stock solutions freshly prepared from different CG capsules by dilution with water to an exact volume. The average of the extinction values thus obtained was used as the reference value in intravital experiments. For each such experiment a fresh stock solution was prepared in precisely the same manner as those used for syringe standardization.

The CG content of what was left in the catheter of the injected indicator was estimated after dilution with physiological saline. Evidently this mode of working included a potential source of error in the cardiac output estimates owing to random variations in the amount of CG powder in the capsules, reportedly  $\pm 10$  per cent of the nominal weight (43).

For Patient 33 the cardilogreen analysis was done as in the new series except that the residue was diluted with physiological saline. The observed extinction value was corrected to dilution with plasma with the aid of an experimentally found conversion factor.

In the early stages of the investigation the mode of blood pressure measurement had not reached its ultimate form. Thus in 7 patients the pressure in the pulmonary artery, left atrium and a systemic artery were recorded separately and in 3 others they were measured simultaneously either before or after the indicator procedure in all 10 patients.

## STATISTICS<sup>1)</sup>

Statistical characteristics were calculated as described in current textbooks for example SÆVREDOSS (127). The formula  $\sqrt{d^2/2n}$  was used for deriving the standard error of a single determination in sets of duplicate determinations whose mean difference was not significant (23).

The significance of differences between means and between coefficients of regression was tested with the aid of STUDENT's  $t$ . Standard deviations were compared by  $F$  testing the corresponding variances. The difference between two one estimated and the other estimated or hypothetical coefficients of correlation was tested with the aid of FISHER's  $z$  transformation. All significances were tested on the 5 per cent level.

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1) Mr. KERSTEN CARLSTRÖM was consulted on choice of methods.

## EVALUATION OF THE METHOD FOR PULMONARY BLOOD VOLUME DETERMINATION

### IMMEDIATE HAEMODYNAMIC EFFECTS OF PULMONARY BLOOD VOLUME DETERMINATION

Since *PBV* determination involves the presence of catheters in the heart, injection of foreign substances and blood loss, it is justified to consider whether the procedure precipitates any immediate haemodynamic effects. These would then be disclosed by analysis of blood pressures and heart rates measured before and after the indicator procedure.

The first *PBV* determination was analyzed for the patients in the new series. In one of them (No 48) no acceptable measurement of the pressure in the left atrium was obtained after blood collection.

The mean heart rate was 75.1 beats per minute before and 70.7 beats per minute after the indicator procedure ( $S_d = 7.0$  beats per min) the difference not being significant. During blood collection the mean heart rate was 74.5 beats per minute. During the indicator procedure the mean blood pressure dropped on average 0.9 mm Hg in the pulmonary artery ( $p < 0.05$ ,  $S_d = 2.0$  mm Hg), 0.6 mm Hg in the left atrium ( $p < 0.05$ ,  $S_d = 1.2$  mm Hg) and 1.4 mm Hg in a systolic artery ( $p > 0.05$ ,  $S_d = 5.0$  mm Hg).

*Comment.* Neither the heart rate nor the systemic arterial pressure was influenced systematically by *PBV* determination. The heart rate estimations in the present study were based upon data recorded during the blood collection and, apart from the fact that such an estimation was concurrent with the *PBV* determination, it should be more accurate since 90 heart beats were taken into account rather than 10 as for the other estimations. The pressure in the left atrium was systematically lower after than before the indicator procedure and the pressure in the pulmonary artery showed a similar and significant reduction. Hence there is reason to suspect that *PBV* determination is accompanied by a small but real haemodynamic disturbance. However the average pressure differences were small, smaller than the accuracy of individual pressure measurements. *PBV* determination involves injection of indicators and with drawal of between 1 and 2 per cent of the total blood volume, but it is not known which of these two procedures was responsible for the fall in pressure. Nor do available data indicate at what phase of the indicator procedure the pressure alteration took place. The averages of the values before and after *PBV* determination of the pressures in the pulmonary

artery left atrium and a systemic artery were presumably in close agreement with the pressures actually prevailing during that procedure. Occasionally in the old series the pressures were measured only before or only after *PBF* determination. From the data presented, it appears that to do so is practically equivalent to giving the averages of the values registered before and after *PBF* determination, as has been done here for the majority of patients.

The validity of the *PBF* estimations is based upon the hypothetical, in practice merely approximately satisfied premises that the blood flow and capacity of the vascular bed remain constant during the measurements (146, 147). This hypothesis cannot be tested directly but the small pressure changes and unaltered heart rates registered in the present study suggest that the double indicator technique does not provoke any immediate haemodynamic changes capable of invalidating the *PBF* determinations.

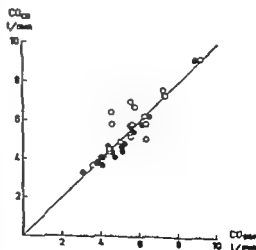
## CARDIAC OUTPUT DETERMINATIONS

The results of the cardiac output determinations were analyzed statistically in order to compare *BSP* and *CG* the pulmonary artery and the left atrium as indicator injection sites as well as the indicator procedure itself and the Fick method. The results of these analyses and the number of patients involved are given in Table 3 on page 27 in which the letters *a* to *k* refer to the similarly lettered sections in the text. The abbreviations used have the meanings shown on page 5.

### *1 Simultaneous BSP and CG Injection into Separate Catheters to Pulmonary Artery and Left Atrium.*

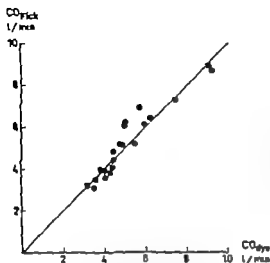
These analyses were based on the cardiac outputs calculated for Patients 35 to 72 in the new series. Clinical and haemodynamic data are presented in Table 11 page 75. Whenever more than one pair of cardiac output determinations at rest was made in the same patient, the results of the first were included in the analysis *a*, *b* *c* and *d* because the experimental conditions applying to the initial determination were most like those applying to patients in whom only a single determination was made.

#### *a. BSP Injection into Pulmonary Artery and CG into Left Atrium (Fig. 1)*



1 Comparison between  $CO_{BSP}$  and  $CO_{CG}$  at *PBF* estimation in 38 patients. Dots denote *BSP* injected into pulmonary artery and *CG* into left atrium (19 patients); circles denote *CG* injected into pulmonary artery and *BSP* into left atrium (19 patients). The line of identity is shown.





Comparison between simultaneous CO estimations by indicator dilution and Fick's method (23 patients).  $CO_{dye}$  denotes the average of simultaneous estimations with BSP and CG. The line of identity is shown.

*b. BSP Injection into Left Atrium and CG into Pulmonary Artery (Fig. 1)*

In analyses *a* and *b* the mean difference is not significant and the regression coefficient does not deviate from unity ( $p > 0.05$ ). In addition the standard deviations of the difference are not unequal ( $p > 0.05$ ).

*c. BSP and CG Injected Regardless of Site (Fig. 1)*

The patients and procedures were those used in Analyses *a* and *b*.

The mean difference is not significant and the coefficient of regression is not significantly separated from unity.

*d. Cardiac Output Determined Simultaneously with Indicators and by Fick's Method (Fig. 2)*

The mean difference is not significant and the coefficient of regression is not significantly separated from unity.

*e. Duplicate Cardiac Output Determinations with BSP and CG (Fig. 3)*

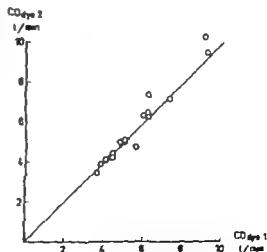
The patients in this group underwent two consecutive determinations at rest (cf p. 32).

Though the mean difference is not significant, the significant deviation from unity of the regression coefficient indicates that the cardiac output tended to be higher on the second occasion at higher flows. This tendency was due to Patients 50 and 63 whose cardiac output was significantly higher the second time.

*f. Duplicate Cardiac Output Determinations with BSP or CG Injected into Pulmonary Artery*

The patients and procedures were identical to those in Analysis *e*.

Neither the mean difference nor the



2 Duplicate CO estimations in 17 patients.  $CO_{dye}$  denotes the average of simultaneous estimations with BSP and CG (cf Figs. 9-10). The line of identity is shown.

deviation from unity of the coefficient of regression are significant.

*g Duplicate Cardiac Output Determinations with BSP or CG Injected into Left Atrium.*

The patients and procedures were those used in Analyses *e* and *f*.

The mean difference is not significant but, as in Analysis *e*, the regression coefficient deviates from unity ( $p < 0.05$ ). The mean difference, the standard deviation of the difference and the regression coefficient in Analysis *g* are not significantly separated from the corresponding quantities in Analysis *f*.

*II Simultaneous BSP and CG Injection into Same Catheter*

In a special study BSP and CG were injected simultaneously into the same catheter the aim being to eliminate as far as possible any haemodynamic factors capable of introducing differences between the results obtained with BSP and CG. These analyses were done on Patients 72 to 90 whose clinical and haemodynamic data will be found in Table 12, page 75.

In this part of the study the residual BSP-CG mixture withdrawn after the injection was analyzed after dilution to 100 ml with blood bank plasma. Apart from Patient 80 who received the first injection in the supine position and the second standing up, all patients were injected in the supine position at rest. The indicators were injected via a three way stop-cock using the same syringes as for PBI determination except for Patients

86 to 90 who received both indicators from a syringe filled from a stock solution of both BSP and CG. The amount of BSP in the syringe was determined in the same way as CG. Blood was collected either from the brachial artery or from the distal aorta. It was estimated that approximately 75 ml of blood was withdrawn per determination.

*h BSP and CG Injected into Pulmonary Artery (Fig 4)*

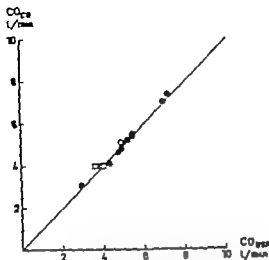
The mean difference is not significant and the coefficient of regression not separated from unity ( $p > 0.05$ ).

*i BSP and CG Injected into Left Atrium (Fig 5).*

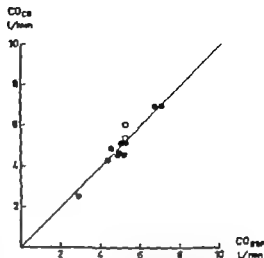
The mean difference is not significant, nor is the coefficient of regression separated from unity ( $p > 0.05$ ). Comparison of Analyses *h* and *i* discloses that whereas the mean differences are not significantly unequal, the standard deviation of the difference in Analysis *i* significantly exceeds that in Analysis *h*.

*III Cardiac Output Determinations with BSP and CG in Old Series*

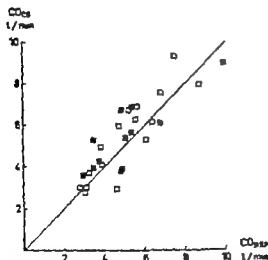
For those patients in the old series whose CG extinction value was read at 780  $m\mu$ ,  $CO_{BSP}$  was compared with  $CO_{CG}$  in conjunction with PBI determination at rest. The group comprised Patient 1 to 34 except No 33 whose CG extinction value was read at 805  $m\mu$ , and Nos 24, 25, 31 and 32, in whom either of the CO estimations failed owing to slight leakage of one of the indicators.



4 Comparison between  $CO_{BSP}$  and  $CO_{CO}$  estimated by injection of both indicators into the pulmonary artery 14 times in 13 patients. Squares denote a patient injected twice into the pulmonary artery; dots denote 10 patients receiving one injection into the pulmonary artery and another into the left atrium (cf. Fig. 5) circles denote two patients given a single injection. The line of identity is shown.



5 Comparison between  $CO_{BSP}$  and  $CO_{CO}$  estimated by injection of both indicators into the left atrium 13 times in 12 patients. Dots denote 10 patients receiving one injection into the left atrium and another into the pulmonary artery (cf. Fig. 4); circles denote two patients given single injection. The line of identity is shown.



6. Comparison between  $CO_{BSP}$  and  $CO_{CO}$  at  $PFV$  estimation in 29 patients in the old series (cf. Fig. 1). Filled squares denote injection of  $BSP$  into pulmonary artery and  $CO$  into left atrium and open squares denote injection of  $CG$  into pulmonary artery and  $BSP$  into left atrium. The line of identity is shown.

#### k. Simultaneous $BSP$ and $CG$ Injection into Separate Catheters in Pulmonary Artery and Left Atrium (Fig. 6)

The statistical analysis is based on the first determination whenever two were made.

The mean difference is not significant, nor does the coefficient of regression deviate from unity ( $p > 0.05$ ).

#### Comment

The validity of the  $BSP$  method for determining cardiac output was demonstrated by WARREN (142) and MILETTTE *et al* (89) who injected simultaneously  $BSP$  and Evans Blue (T 1824) into the same catheter inserted either into the pulmonary artery or into a peripheral

Table 2. Evaluation of cardiac output estimations. Analyses to 2 refer to similarly coded sections of text on pp. 22 to 24

| Analysis  | No. of patient | x     | y     | z     | $\beta$ | $\beta_d$ | $\eta_d$ | $b_{yz}$ | $\delta_b$ | $\delta_r$ | r <sub>z</sub> | $\delta$ | $\frac{\delta_d}{2+y} \times 100$ |
|---|----------------|-------|-------|-------|---------|-----------|----------|----------|------------|------------|----------------|----------|-----------------------------------|
|   |                | l/min | l/min | l/min | l/min   | l/min     | l/min    |          |            | l/min      |                |          | per cent                          |
| 1. BSP in P 1 (7) in L 1 = CO <sub>BSP</sub><br>y = CO <sub>CO</sub>                        | 19             | 5.07  | 4.9   | +0.09 | 0.18    | 0.84      | 0.84     | 0.88     | 0.8        | 0.8        | 0.94           | 0.04     | 10.7                              |
| 2. BSP in L 1 (7) in P 1 = CO <sub>BSP</sub><br>y = CO <sub>CO</sub>                        | 19             | 5.54  | 5.74  | -0.20 | 0.17    | 0.74      | 0.74     | 0.81     | 0.13       | 0.73       | 0.88           | 0.12     | 12.1                              |
| 3. Litter data in P 1 other in L 1 = CO <sub>BSP</sub><br>y = CO <sub>CO</sub>              | 28             | 5.80  | 5.88  | -0.07 | 0.11    | 0.85      | 0.85     | 0.91     | 0.07       | 0.84       | 0.90           | 0.7      | 12.8                              |
| 4. = CO <sub>BSP</sub> y = CO <sub>P 1</sub>  | 23             | 5.85  | 5.84  | -0.11 | 0.11    | 0.85      | 0.85     | 1.00     | 0.08       | 0.85       | 0.4            | 0.07     | 10.4                              |
| 5. Dupile determ. = CO <sub>BSP</sub> y = CO <sub>BSP</sub>                                 | 17             | 5.88  | 5.75  | -0.17 | 0.11    | 0.87      | 0.87     | 1.14     | 0.04       | 0.86       | 0.88           | 0.08     | 8.3                               |
| 6. Dupile determ. = CO <sub>P 1</sub> y = CO <sub>P 1</sub>                                 | 17             | 5.79  | 5.80  | -0.10 | 0.11    | 0.84      | 0.84     | 1.05     | 0.7        | 0.43       | 0.97           | 0.86     | 7.7                               |
| 7. Dupile determ. = CO <sub>L 1</sub> y = CO <sub>L 1</sub>                                 | 17             | 5.48  | 5.78  | -0.29 | 0.15    | 0.80      | 0.80     | 1.18     | 0.04       | 0.88       | 0.97           | 0.07     | 10.8                              |
| 8. BSP and CO in P 1 = CO <sub>BSP</sub> y = CO <sub>CO</sub>                               | 12             | 4.98  | 4.98  | -0.07 | 0.08    | 0.17      | 0.17     | 1.00     | 0.01       | 0.17       | 0.99           | 0.4      | 2.4                               |
| 9. BSP and CO in L 1 = CO <sub>BSP</sub> y = CO <sub>CO</sub>                               | 12             | 5.8   | 5.88  | 0.09  | 0.11    | 0.8       | 0.8      | 1.08     | 0.11       | 0.97       | 0.95           | 0.10     | 7.8                               |
| 10. Old series, 1 liter dye in P 1 other in L 1<br>= CO <sub>BSP</sub> y = CO <sub>CO</sub> | 22             | 5.38  | 5.43  | -0.11 | 0.18    | 0.8       | 0.8      | 0.90     | 0.09       | 0.88       | 0.88           | 0.09     | 17.8                              |

vein. In recent years Cardilogreen (CG) brand of Indocyanine green, has acquired widespread use as an indicator. Its properties have been summarized by FOX & WOOD (43) and HUNTON *et al* (67). SMULYAN (126) investigating the blood flow in dogs injected simultaneously CG and  $^{125}\text{I}$  labelled serum albumin (RISA) in the right atrium and collected blood from the carotid artery. There was no systematic difference between the two methods.

BSP and CG both have very low toxicity and are rapidly removed from the blood by the liver enabling repeated injections to be made at comparatively short intervals. Since both these indicators are bound to the plasma albumin, their modes of mixture and transport in the blood stream are similar.

The extinction curve for rising BSP concentrations is linear and it makes no difference whether the diluent is plasma or physiological saline justifying the use of the latter diluent for standardization and analysis of residual indicator. The extinction curve for rising CG concentrations in plasma on the other hand, was found to be slightly non linear but the CG extinction values of interest in cardiac output determinations were below the level where this non linearity becomes an appreciable factor. It has also been shown that whole blood dilutions of CG exhibit a similar slight non linearity (43-68).

Irrespective of whether they are injected into the same catheter or into separate catheters to the pulmonary artery and left atrium, simultaneously injected BSP and CG will have dilution curves that wholly or partly overlap in other words some of the fractionated blood samples

collected will contain a mixture of BSP and CG. Clearly therefore, the simultaneous use of BSP and CG precludes that neither indicator interferes with estimation of the other. Dilution experiments whose results are set out in Table 4 and the very close agreement between  $\text{CO}_{\text{BSP}}$  and  $\text{CO}_{\text{CG}}$  when the two indicators were injected simultaneously into the pulmonary artery (Analysis A) bear out the assumption that the indicators could be estimated independently. The standard deviation of the difference in Analysis A is smaller than those WASSER and MILLER *et al* found using BSP and T 1824 and also smaller than that found by SMULYAN using CG and RISA.

The lack of significant differences between  $\text{CO}_{\text{BSP}}$  and  $\text{CO}_{\text{CG}}$  after injection into the same catheter to the pulmonary artery or left atrium (Analyses A and i) or after injection into separate catheters to the pulmonary artery and left atrium, when distinction was made between these injection points (Analyses a and b) suggest that neither BSP nor CG disappears from the blood during passage through the lungs. Since there was no systematic difference between the pulmonary artery and left atrium as injection points (Analyses a and b) shunts from the pulmonary circulation to the bronchial vessels were unlikely to constitute a source of systematic error for then  $\text{CO}_{\text{PA}}$  would have exceeded  $\text{CO}_{\text{LA}}$  because part of the indicator volume injected into the pulmonary artery would have disappeared via the bronchial vessels.

The assumed validity of the indicator procedure is based upon studies in most of which the indicator has been injected somewhere upstream of the pulmonary

Table 4. A dilution experiment illustrating that neither bromsulphalein (*BSP*) nor cardiogreen (*CG*) interferes materially with the spectrophotometric estimation of the other. The optical density (*O.D.*) was found for six samples from each flask.

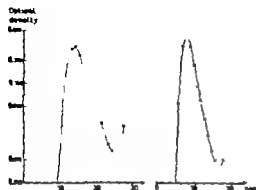
| Sample | Volum. flask I<br>1 ml <i>CG</i><br>Plasma to 100 ml |                          | Volum. flask II<br>1 ml <i>BSP</i><br>Plasma to 100 ml |                          | Volum. flask III<br>1 ml <i>CG</i> +1 ml <i>BSP</i><br>Plasma to 100 ml |                          |
|--------|--|--------------------------|--|--------------------------|---|--------------------------|
|        | <i>BSP</i><br><i>O.D.</i>                            | <i>CG</i><br><i>O.D.</i> | <i>BSP</i><br><i>O.D.</i>                              | <i>CG</i><br><i>O.D.</i> | <i>BSP</i><br><i>O.D.</i>   | <i>CG</i><br><i>O.D.</i> |
| 1      | 0  | 255                      | 1.188  | 009                      | 1.188   | 252                      |
| 2      | 0  | 290                      | 1.198  | 007                      | 1.198   | 282                      |
| 3      | 0  | 265                      | 1.188  | 007                      | 1.190   | 282                      |
| 4      | 0  | 290                      | 1.196  | 007                      | 1.190   | 282                      |
| 5      | 0  | 290                      | 1.194  | 008                      | 1.188   | 280                      |
| 6      | 0  | 288                      | 1.190  | 005                      | 1.186   | 282                      |
| mean   | 0  | 289                      | 1.192  | 007                      | 1.190   | 282                      |

capillary bed and collected from a systemic artery. In such circumstances mixture takes place in the lungs and either or both halves of the heart, and this is considered approximately to satisfy the requirement for uniform mixing of the indicator and blood. When *BSP* and *CG* are injected simultaneously into the same catheter they measure the same flow and are subject to the same errors of method due to departures from the theoretically postulated state of constant haemodynamics so biological variation will not contribute to any differences between the results. The significantly greater standard deviation of the difference after injection of *BSP* and *CG* into the left atrium (Analysis *g*) than into the pulmonary artery (Analysis *k*) could be contingent upon somewhat inferior mixing of blood and indicator in the former case. If all injections on the venous side — pulmonary artery (Fig. 4) right atrium or inferior caval vein (Table 1 on page 75) — are compared with all injections into the

left atrium (Fig. 5), the difference in dispersion of the points about the line of identity becomes even more pronounced. Yet even if real the difference is small, and in duplicate cardiac output determinations the variations were not significantly greater after injection into the left atrium (Analysis *g*) than into the pulmonary artery (Analysis *j*).

After simultaneous injection of *BSP* and *CG* into separate catheters the standard deviation of the difference between  $CO_{BSP}$  and  $CO_{CG}$  will include biological variation and the errors of method due to inconstant haemodynamics will not be the same for the two indicators. For *BSP* and *CG* then do not pass the same circulatory pathways concurrently. This explains why the standard deviation of the difference was much greater when *BSP* and *CG* were injected into separate catheters (Analyses *a*, *b*, *c* and *k*) than into the same catheter (Analyses *d* and *j*).

Compared with injection of indicators into the pulmonary artery injection in



7 A typical example in which the patients received similar  $CO$  amounts into the pulmonary artery (left curve) and the left atrium (right curve). Note that right dilution curve is taller narrower and shows relatively later recirculation than left dilution curve.

the left atrium tended to yield higher and narrower based dilution curves with relatively somewhat delayed commencement of recirculation. This could be explained by the fact that an indicator injected into the left atrium is diluted in a smaller blood volume than one injected into the pulmonary artery. Notably however injection into the left atrium did not abnormally distort the dilution curves, as might have been expected after inadequate mixing (Fig 7).

The absence of systematic differences between  $CO_{PA}$  and  $CO_{LA}$  in Analysis d bears out the assumption that within their range of accuracy the indicator procedure and the Fick method both correctly measured true blood flow and that shunts between the bronchial arteries and the pulmonary circulation were not quantitatively important. FARRIS *et al* (47) demonstrated that one should expect such shunts to give rise to systematic differences between the Fick method and

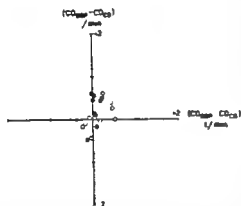
the indicator dilution procedure when blood is collected from a systemic artery.

The dispersion of the differences between  $CO_{BSP}$  and  $CO_{CG}$  after simultaneous injection into the aorta or separate catheters (Figs 1 4 5 and 6) did not tend to increase with increasing flow implying that the relative dispersion diminished with increasing flow. Nor did DOCK *et al* or OAKLEY *et al* (25 99) find any increase in the dispersion of the differences between  $CO_{PA}$  and  $CO_{LA}$  with increasing flows when they determined the pulmonary blood volume in the same type of patients as those of the present investigation. In patients with low flow associated with valvular disease and cardiac enlargement the chances of adequate mixing of indicator and blood are probably poorer than in normal subjects. The disappearance slope of their dilution curves becomes flatter and the recirculation starts at a relatively higher level than in normals causing the extrapolation error to rise. These factors might contribute to produce a relative increase of the dispersion with decreasing flows.

When  $BSP$  and  $CG$  were injected simultaneously into separate catheters to the pulmonary artery and the left atrium the difference between  $CO_{BSP}$  and  $CO_{CG}$  tended to recur and be similar in magnitude and direction following repeated injections to the same patient (Fig 8). Whether haemodynamic factors or the analysis of the indicators were responsible cannot be deduced from the data presented here but trials are in progress in which the same patient undergoes repeated indicator procedures with alternating points of injection of  $BSP$  and  $CG$  the results so far suggesting that the differ

ence tends to accompany the points of injection rather than the indicators. As this phenomenon seems to be of fundamental importance to the indicator procedure as such it will become the subject of further study. Differences between  $CO_{Fick}$  and the average of  $CO_{RSP}$  and  $CO_{CG}$  showed no tendency to recur more often than could be accounted for by random variation.

For the purposes of  $PBV$  determination DOCK *et al* (25) simultaneously injected Evans blue (T 1824) into the pulmonary artery and  $^{125}I$  labelled human serum albumin (RISA) into the left atrium. They found no systematic difference between  $CO_{PA}$  and  $CO_{LA}$  nor there fore between the two indicators. The average ratio of the flows was 0.98 with a standard deviation of 0.18.



8. The difference  $CO_{RSP} - CO_{CG}$  in 36 patients from the new series at rest plotted against the corresponding differences on subsequent occasions in the same patients at rest in 17 (dots) and during exercise or voluntary hyperventilation or CO-breathing in 19 (crosses). Index of injection points—pulmonary artery and left trans-aorta—alternated but even but not within patient. The coefficient of correlation ( $r = 0.74$ ) is significant.

OAKLEY *et al* (89) at short intervals injected  $CG$  into the pulmonary artery and into the left atrium in random order without finding any significant difference between  $OI_{PA}$  and  $OI_{LA}$  (Cardiac Index). The standard deviation of the difference was 0.48 litres per minute per square metre body surface area, the coefficient of correlation being specified in a subsequent paper (145) as 0.90.

MCGARR *et al* (86) also injecting  $CG$  twice in rapid succession, reported that  $CO_{LA}$  significantly exceeded  $CO_{PA}$  but the mean difference was merely 4 per cent which could be due to the fact that the flows were not measured concurrently. In their first investigation (90) there was a similar small systematic difference between  $CO_{PA}$  and  $CO_{LA}$ .

The fact that indicator passage through half the heart gives rise to adequate mixing and permits correct cardiac output estimations was demonstrated by FARRIS *et al* (46). After injecting an indicator into the right atrium of nine normals they estimated the cardiac output by simultaneous blood collection from the pulmonary and brachial arteries. The results were compared with those obtained by Fick's method. None of the ratios  $CO_P / CO_{PA}$  and  $CO / CO_{Fick}$  exceeded  $1.0 \pm 0.15$  nor did the mean ratios deviate systematically from unity. BARNHARTWRIGHT *et al* (8) reported similar results of estimation in dogs with indicator injected into the inferior vena cava and blood collection simultaneously from the pulmonary artery and two systemic arteries.

Considering that the very same  $RSP$  procedure was used in the old series and the new series the lack of any systematic difference between  $CO_{RSP}$  and  $CO_{CG}$  in the



old series (Analysis k) suggests that neither did the two dissimilar *CG* procedures differ systematically. Hence estimations of *CO* as the average of  $CO_{BSP}$  and  $CO_{CO}$  using the "old *CG* procedure may be assumed not to differ systematically from the corresponding estimations of flow based on the new" *CG* procedure. Because the differences between  $CO_{BSP}$  and  $CO_{CO}$  were larger in the old series (Analysis k) than in the new (Analysis c) it may similarly be assumed that *CG* measured blood flow less accurately in the old series and consequently that the standard error of a single determination for the mean of  $CO_{BSP}$  and  $CO_{CO}$  in the old series was somewhat larger than in the new series. In its ultimate form the *CG* method adopted in the present investigation was evolved from a procedure that has not been described previously. It was found by means of dilution experiments that the use of anything other than whole plasma for standardization and analysis of residual *CG* gave rise to various small errors which were impossible to analyze retrospectively in the individual case. Quite empirically however it was ascertained that these errors did not introduce systematic discrepancies when the *BSP* and *CG* methods were compared.

In the light of the foregoing it appears that indicators injected into the left atrium become adequately mixed with the blood during their passage through the left heart and enable correct determinations of cardiac output. The mean of the two simultaneous estimations of blood flow—used here for calculation of pulmonary blood volume—may be assumed not to differ systematically from the actual blood flow.

## DUPLICATE PULMONARY BLOOD VOLUME DETERMINATIONS

In 20 patients from the new series two consecutive *PBV* determinations were made at rest. In Patient 42 a small *BSP* leakage occurred during the first procedure but this did not prevent  $MTT_{pulm}$  and hence *PBV* to be found with the aid of  $CO_{CO}$ . *PBV* of Patients 40 and 41 was determined before and after a period of voluntary hyperventilation. The duplicate *PBV* determinations as well as other factors estimated at the same time, were analyzed statistically for the remaining 17 patients. Patient 48 was excluded from analysis of left atrial pressure, pulmonary vascular pressure drop and *P/R* because of unsuccessful attempts to record the left atrial pressure after the initial indicator procedure. Occasionally the arteriovenous oxygen difference or the ventilation and oxygen consumption were not measured in conjunction with both *PBV* determinations. Any results of the statistical analysis not specified in the following will be found in Table 5 on page 33.

**Results** The pulmonary blood volumes have been plotted in Fig. 8 showing that the points are uniformly distributed about the line of identity but tend to be more widely dispersed with rising *PBV*. Consequently the pulmonary blood volumes to be compared were expressed as ratios which were assumed to have an approximately normal distribution (127). Mean  $PBV_1 = 563$  ml, mean  $PBV_2 = 575$  ml,  $PBV_2/PBV_1 = \bar{r}$ ,  $\bar{r} = 1.02$ ,  $S_1 = 0.02$ ,  $S_2 = 0.10$ . Duplicate *PBV* determinations did not deviate systematically.

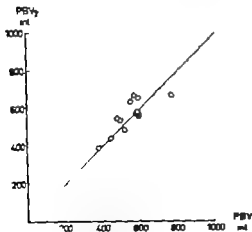
The mean transit times were also uniformly distributed about the line of identity.

Table 3. Duplicate determinations of factors measured simultaneously with duplicate  $PBF$  estimations in 17 patients. ( $x$  denotes the first and  $y$  the second estimation.)

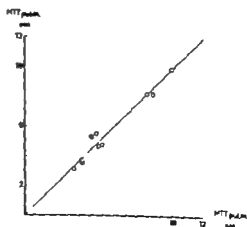
| Factor   | No. of patients | $x$  | $y$  | $d$   | $S_d$ | $S_y$ | Patients outside $2 \pm 2 S_d$ |
|--|-----------------|------|------|-------|-------|-------|--------------------------------|
| $P_p$ mm Hg  | 17              | 31.1 | 30.6 | 1.1   | 0.3   | 2.2   | 47 62                          |
| $P_{LA}$ mm Hg                                       | 16              | 11.9 | 10.  | +1.3  | 0.3   | 1.3   | 47 6.                          |
| $(P_p - P_{LA})$ mm Hg                               | 16              | 9.7  | 8.7  | 0     | 0.    | 1.7   | 53                             |
| $P_{Ave}$ mm Hg                                      | 17              | 83.4 | 80.  | +1.7  | 1     | 5.8   | 47                             |
| Palm. vasa. res. ( $P_{VRA}$ ) mm Hg l/min           | 16              | 1    | 2.9  | 0     | 0.    | 0.3   | 53                             |
| Heart rate ( $HR$ ) beats/min                        | 17              | 81   | 80.9 | +0.9  | 1.6   | 6.3   | 47                             |
| Stroke volume ( $SV$ ) ml                            | 17              | 1.4  | 74.6 | -2.6  | 1.6   | 8.4   | 47 50                          |
| Art. O <sub>2</sub> -satur. ( $Se_{O_2}$ ) per cent  | 16              | 97.8 | 97.9 | +0.2  | 0.3   | 1     | 47 63                          |
| Art. en. O <sub>2</sub> -diff. ( $a-v_{O_2}$ ) ml/l  | 14              | 4.1  | 47.1 | 0     | 0.6   | 3.3   | 5.                             |
| O <sub>2</sub> -consum. ( $\dot{V}_{O_2}$ ) ml/min   | 13              | 244  | 249  | -5    | 4     | 15    | 62                             |
| Ventilation ( $\dot{V}_E$ ) l/min                    | 13              | 7.3  | 7.7  | -0.3  | 0.3   | 1.6   | 49                             |
| Card. output $_{P_{VRA}}$ ( $CO_{P_{VRA}}$ ) l/min   | 14              | 3.39 | 3.73 | -0.14 | 0.17  | 0.63  | 58                             |
| Card. output $_{d_{pO_2}}$ ( $CO_{d_{pO_2}}$ ) l/min | 17              | 3.54 | 3.72 | -0.17 | 0.11  | 0.47  | 50 63                          |

ty as shown in Fig 10 Mean  $MTT_{pulm} = 6.62$  secs., Mean  $MTT_{pulm} = 6.62$  secs.  $MTT_{pulm}/MTT_{pulm} = 9.7 \pm 1.00$   $S_d = 0.03$   $S = 0.11$  Duplicate  $MTT_{pulm}$  determination did not differ systematically

The cardiac outputs are presented in Fig 3 and are the same as those in Analysis 2 of Table 3 on page 27. The standard deviation of difference between duplicate cardiac output determinations at rest is 11.47 litres per minute or 8.3 per cent of



Duplicate  $PBF$  estimation 17 patients (cf. Figs. 3, 10). The line of identity is shown.



Duplicate  $MTT_{pulm}$  estimations in 17 patients (cf. Figs. 3, 8). The line of identity is shown.

the mean cardiac output, corresponding to a standard error of a single determination of 0.34 litres per minute or 6.0 per cent of the mean cardiac output. The results of duplicate determinations by the Fick method were similar to those of the indicator technique. Thus the cardiac outputs of 14 patients in Analysis *c* were also determined twice by the Fick method. The mean difference is not significant and the standard deviation of difference amounts to 0.63 litres per minute corresponding to 11.1 per cent of the mean output (Table 5).

Among the other measurements made three exhibited significant changes. Thus the mean pressure fell on average 1.1 mm Hg ( $p < 0.05$ ) in the pulmonary artery, 1.3 mm Hg ( $p < 0.05$ ) in the left atrium and 2.7 mm Hg ( $p < 0.05$ ) in a systemic artery.

No significant systematic changes were disclosed by duplicate determinations of pulmonary vascular pressure, fall pulmonary vascular resistance, heart rate, stroke volume, arterial oxygen saturation, arteriovenous oxygen difference, oxygen consumption and ventilation (Table 5).

**Comments:** The presence of a number of catheters in central parts of the circulation constitutes a potential risk for haemodynamic disturbances, induced through direct mechanical irritation by the catheters or by the patient being upset by the examination. This must reduce the concept at rest to an approximation of basal conditions. WADE & BISHOP (139) having surveyed the relevant literature maintained that the direct Fick procedure rarely changes the cardiac output. The double indicator technique imposes greater strain on both

physician and patient in addition to involving blood withdrawal and injection into the organism of foreign indicator substances, all of which might well give rise to haemodynamic manifestations. Against this background, the haemodynamic changes associated with duplicate *PBF* determinations were surprisingly small. The average pressures recorded in the pulmonary artery, left atrium and a systemic artery were indeed lower when the second *PBF* determination was made but only slightly so, and whatever real haemodynamic changes these alterations might have reflected must have been negligible as the cardiac output, heart rate and stroke volume were not systematically affected. The reproducibility of cardiac output determinations by the indicator dilution technique was of a similar order as those reported by other workers (22, 14, 86). The average pressure drops in the pulmonary artery and left atrium were of the same order, about 1 mm Hg as the pressure fall recorded in the pulmonary circulation immediately following the first indicator procedure in the new series (p. 22). Either the indicator injections or the blood losses could be responsible for the pressure changes on both occasions.

Factors contributing to the variation of duplicate *PBF* determinations include errors of method and biological variation. In Patient 47 a real haemodynamic alteration no doubt did occur as may be deduced from the changes in blood pressure as well as in heart rate and stroke volume. And, because the oxygen consumption remained substantially unchanged, the increased ventilation attending the second procedure in Patient 48 was probably not

due to expired-air leakage. A positive correlation probably exists between changes in  $PBI$  and in stroke volume (51) and it has been demonstrated that hyper-ventilation increases  $PBF$  (104). Consequently part of the  $PBI$  increase observed at the second indicator procedure in Patient 47 and 48 might be real and associated with the concomitant increases in stroke volume and ventilation respectively. Patient 54 hyperventilated at both measurements as verified by estimation of arterial  $CO$  tension.

The duplicate  $PBF$  determinations for those three patients not included in the statistical analysis were closely similar the differences in  $PBF$  being 0, 13 and 8 ml. In the old series duplicate  $PBI$  determinations were made at rest in Patient 9 the difference in  $PBI$  being 14 ml. Had these four patients all been included in the statistical analysis the standard deviation of the ratio  $PBI_2/PBI_1$  would have been slightly less than 0.1.

Information on duplicate  $PBI$  determinations with the aid of the double indicator technique is very scanty. McGARR *et al* (86) made duplicate determinations in 30 dogs and found that the standard deviation of the difference was 10 per cent of the mean. Reporting the results of duplicate  $PBI$  determinations in 16 patients with various cardiovascular disorders YU *et al* (145) obtained a standard deviation of the difference amounting to 14.9 ml per square metre body surface area which — judging by their graph — corresponded to about 5 per cent of the mean  $PBI$ . This is a somewhat smaller variation than that in the present investigation but a YU *et al* (145) gave no particulars of their individual measure-

ments no conclusions can be drawn about what might be the cause of this discrepancy.

## SOURCES OF ERROR

An assessment of the consequences of the dissimilar  $CG$  methods for  $CO$  estimation used in the old and the new series is presented on p. 31. It is shown that when cardiac output is determined as the average of  $CO_{BSP}$  and  $CO_{CG}$  the old series deviated from the new series in having a slightly larger standard error of a single determination.  $MTT_{pul}$  was consistently estimated in the same manner so the difference between the old and the new series in the methods of determining  $PBF$  should be confined to the somewhat larger standard error of a single determination in the former series with no contribution from systematic differences between the methods. Hence it should be permissible to compare or combine the two series.

The accuracy of the indicator technique for  $PBF$  determination is as good as the estimations of cardiac output and mean transit time. Its validity in cardiac output determinations have been demonstrated already. A number of workers have dealt with the potential errors in  $PBF$  determinations by the double indicator technique (25, 51, 87, 90, 99). The arterial dilution curve is the outcome of the transport of blood and indicator through the circulation and the blood collection system whose effects upon the dilution curve one wishes either to eliminate or to render negligible.

In the method of  $PBF$  determination under discussion here the processes of injecting  $BSP$  and  $CG$  may be assumed to

have equal durations. Although the indicator passages through the collecting catheter are not exactly concurrent the dilution curves partly overlap and, regardless of the type of flow in the catheter its mean transit time for *BSP* may be assumed approximately equal to that for *CG*. Hence we may write

$$\begin{aligned} (MTT_{br,prox} + MTT_{PA-A} + MTT_{cor}) - \\ - (MTT_{br,prox} + MTT_{LA-A} + MTT_{cor}) = \\ = MTT_{PA-A} - MTT_{LA-A} = MTT_{PA-LA} \\ = MTT_{perf} \end{aligned}$$

In the present investigation blood was collected from the brachial artery or the distal part of the aorta, via catheters of rather different types with dissimilar internal diameters, lengths and capacities. To test the hypothesis that the collecting catheter did not influence the *PBI* determination, the pulmonary blood volume of Patient 70 was determined with an 18 cm long catheter in the brachial artery and a 100 cm long catheter in the distal aorta, the object being to exaggerate the ordinary catheter differences. The results of two determinations at rest with an interval of 90 minutes are set out in Table 6. It shows that practically identical *PBI* determinations were made with blood collection from two different arteries via catheters of very dissimilar dimensions, the corresponding values for  $MTT_{min}$  and *CO* also agree closely.

Similar results have been obtained in a series of *PBI* determinations in seven patients at which blood was collected simultaneously from the brachial artery via a 40 cm long catheter and from the distal aorta via a 98 cm long catheter (134)

Table 6. *T* & *PBI* estimations at rest in Patient 70 with blood collected simultaneously from the brachial artery (short catheter) and the distal aorta (long catheter)

| Procedure            | Blood collection point | Cardiac output l/min |           |      | Mean transit time sec. |               |       |       | Circ. blood volume ml |               |       |
|----------------------|------------------------|----------------------|-----------|------|------------------------|---------------|-------|-------|-----------------------|---------------|-------|
|                      |                        | <i>BSP</i>           | <i>CG</i> | Mean | <i>PA Art</i>          | <i>LA Art</i> | Pulse | Pulse | <i>PA Art</i>         | <i>LA Art</i> | Pulse |
| Procedure No. 1 Mean | Brach art Aorta        | 84                   | 7.12      | 7.14 | 10.36                  | 3.77          | 4.39  | 4.39  | 1240                  | 690           | 600   |
|                      |                        | 7.34                 | 7.44      | 7.40 | 12.76                  | 8.84          | 4.43  | 4.43  | 1372                  | 1029          | 848   |
|                      |                        | 7.39                 | 7.39      | 7.38 |                        |               | 4.81  | 4.81  |                       |               | 848   |
| Procedure No. 2 Mean | Brach art Aorta        | 7.15                 | 6.88      | 7.02 | 10.43                  | 8.08          | 3.46  | 3.46  | 1228                  | 584           | 633   |
|                      |                        | 7.48                 | 7.4       | 7.39 | 12.93                  | 7.77          | 5.14  | 5.14  | 1380                  | 933           | 836   |
|                      |                        | 7.42                 | 6.97      | 7.19 |                        |               | 5.39  | 5.39  |                       |               | 834   |

These dimensions of the collecting catheters were used for *PBI* determination in the old series as well as in the new series. The differences in *CO*, *MTT<sub>pulm</sub>* and *PBI* at initial estimations at rest between brachial artery and distal aorta collection were calculated for each patient. It appeared that the *CO* difference was 0.6 litres per minute or less (mean = +0.63 l/min.) the *MTT<sub>pulm</sub>* difference was 0.23 seconds or less (mean = -0.03 secs.) and the *PBI* difference was 32 ml or less (mean = +4 ml).

Accordingly there are good grounds for supposing that the collecting catheter has no influence on the *PBI*, *MTT<sub>pulm</sub>* and *CO* estimations, provided the blood is collected under its own pressure and flows sufficiently fast.

So long as the ratio of vascular volume to blood flow is the same in different lung segments it is immaterial for the *PBI* determination if the indicator injected into the pulmonary artery is not distributed to its branches in proportion to their flow. Conversely if this ratio is not the same in different parts of the lungs the attendant source of error will be eliminated if the indicator is uniformly mixed with the blood before the pulmonary artery begins to ramify (76). Regional disproportions between vascular volume and blood flow may presumably exist in patient with abnormalities of the pulmonary vessels. To reduce to a minimum the effects of this source of error the tip of the catheter to the pulmonary artery was located immediately above the pulmonary valves and had a closed terminal aperture and four lateral holes distributing the indicator radially in different directions. This mode of injection should

result in much better immediate mixing than injection of the indicator through a single end hole in the direction of blood flow a mode whereby the indicator must have excellent chances of being distributed unequally to the two lungs.

In patients of the type used for the present investigation, the quantitative significance of anastomoses between the bronchial and pulmonary circulations is probably slight (p. 28 and 30).

The premises underlying *PBI* determination include the assumption that indicator injected into the left atrium will be uniformly mixed therein. MILNOR *et al*, DICK *et al* and OAKLEY *et al* (25, 90, 99) were agreed that departures from this assumption of unknown extent might be a reality. When the pulmonary artery and the left atrium were compared with respect to their suitability as points for injection of indicators (p. 23) it was apparent that the mixing hardly could be very bad. The distal lateral hole in the catheter to the left atrium was designed to facilitate indicator mixing. The catheter to the left atrium could not for technical reasons be provided with multiple lateral holes and a closed terminal hole like the catheter to the pulmonary artery.

The observed pulmonary plasma volume was converted to pulmonary blood volume with the aid of big vessel hematocrit without correcting for the trapped plasma volume which reportedly varies between 0 and 5 per cent of the observed hematocrit, depending on the centrifugal force the duration of centrifugation and the hematocrit level (18, 100, 135, 136). In view of the high centrifugal force of 3600 g used for centrifugation in the

present investigation, the trapped plasma volume presumably was nearer 2 than 5 per cent. Correction for trapped plasma may be done with the aid of the following formula.

$$PBF_{corr} = PBF_{uncorr} \frac{1-H}{1-H(1-y)}$$

where

$PBF_{uncorr}$  =  $PBF$  uncorrected for trapped plasma determined as in the present investigation,

$PBF_{corr}$  =  $PBF$  corrected for trapped plasma,

$H$  = Observed hematocrit level,

$y$  = Trapped plasma volume expressed as a fraction of observed hematocrit

Experimental studies on dogs have demonstrated that the  $MTT_{plasma}$  for plasma is slightly longer than for red cell and also that the organic hematocrit of the lungs is a little lower than big vessel hematocrit (91 79 103 109) PARRISH *et al* (103) found that the ratio of hematocrit of the lungs to hematocrit of the big vessels was 0.93 in open-chest dogs. The exact value of this ratio in man is not known, but it should presumably be of the same order as in dogs, implying that a  $PBF$  measurement made with the aid of plasma indicators will be slightly excessive. LILIENTHAL *et al* (82) studied this matter in cardiovascularly normal subjects by injecting radioactively marked blood corpuscles and  $^{125}I$  labelled albumin either into a peripheral vein or into the pulmonary artery and collecting blood from the femoral artery. Regardless of the site of injection they found no significant

deviation from unity of the mean ratio of hematocrit of the circulating central blood volume to big vessel hematocrit (0.99 0.98) perhaps owing to the fact that  $MTT_{plasma}$  constituted merely part of the  $MTT$  measured in their experiments. Their findings nevertheless disclose that hematocrit of the lung cannot deviate appreciably from big vessel hematocrit in man. Similarly studying patients with mitral stenosis, RAFAPOUR *et al* (110) found that the aforementioned hematocrit ratio did not differ significantly from unity (0.97).

$PBF$  measured with plasma indicators may be corrected for deviations between hematocrit of the lungs and big vessel hematocrit with the aid of the expression.

$$PBF_{corr} = PBF_{uncorr} \frac{1-H}{1-zH}$$

where

$PBF_{uncorr}$  =  $PBF$  uncorrected determined with plasma indicators;

$PBF_{corr}$  =  $PBF$  corrected for hematocrit of the lungs;

$H$  = Observed big vessel hematocrit corrected for trapped plasma,

$z$  = Hematocrit of lungs/hematocrit of big vessels.

Suppose for example we have the following data  $PBF$  measured with plasma indicators = 540 ml, observed big vessel hematocrit = 0.45 trapped plasma = 0.02 times observed hematocrit, and the ratio of hematocrit of the lungs to hematocrit of the big vessels = 0.95. Then  $PBF$  corrected only for trapped plasma will be 530 ml and after correction for

trapped plasma as well as for hematocrit of the lungs it will be 51 ml. The exact validity of the assumptions made in this example is an open question but the calculations do provide an impression of how the corrections affect the *PBI* determination.

In Patients 35 and 42 there were grounds for suspecting that the *PBI* determinations had been influenced by errors of method.

Patient 35 whose *PBI* was extremely large suffered from severe mitral valvular insufficiency which combined with low blood flow caused the indicator injected into the pulmonary artery to show a bad dilution curve with a blunt peak and very flat disappearance slope with no indication of recirculation during collection. Curves of this type do not lend themselves to adequate elimination of the recirculation by means of extrapolation. The blood flow will be underestimated and the mean transit time overestimated when recirculating indicator is included in the area of the extrapolated dilution curve. The fact that the dilution curve for the indicator injected into the left atrium was of better quality with a steeper disappearance slope and distinctly marked recirculation, suggests that it might have been subject to smaller errors in the *CO* and *MTT* estimations. The aforementioned factors could be responsible for the large discrepancy between  $CO_{ASP}$  and  $CO_{CS}$ .  $MTT_{pul}$  as well as *PBI* were probably overestimated. DOCK *et al.* and OAKLEY *et al.* (25-29) adduced that mitral valvular insufficiency was not accompanied by an

excessive *PBI* although DOCK *et al.* admitted that they had been forced to reject several cases of advanced mitral valvular regurgitation because the "prolonged nature of the dilution curves made it difficult to define the exponential decay portion of the curve in the presence of recirculating indicator".

In Patient 42, whose *PBI* was the smallest in the entire new series the extracorporeal phases of the examination procedure and the dilution curves were satisfactory but X ray examination revealed that the large myxoma in the left atrium deflected the catheter tip towards the inlets of the pulmonary veins, suggesting that the indicator probably was injected into one of them. Most likely therefore some of the pulmonary vein blood failed to be included in the estimated *PBI* making the latter too small.

Patients 35 and 42 were at first included in all analyses of relationships between *PBI* and other factors, but they consistently differed from the remainder of the patients. With or without these patients, however the results were similar in principle. As a matter of fact the *PBI* deviated in a direction opposite to what one would expect only in Patient 42. In order to avoid the necessity of having to repeat that the deviating *PBI* of Patients 35 and 42 probably were due to errors of method these subjects were excluded from the analyses but their clinical and haemodynamic data are specified in Table 11. These cases may serve as contributions to the debate on potential errors of method in *PBI* determinations.



## PULMONARY BLOOD VOLUME AND ITS RELATIONS TO OTHER FACTORS AT REST

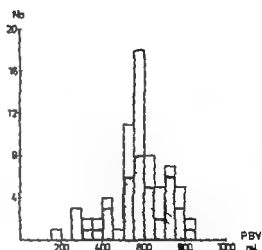
From the old series Patients 1 to 33 were included while No. 34 was eliminated because *PBI* was determined during infusion of metaraminol (Aramin); from the new series Patients 36 to 72 were included while Nos. 35 and 42 were eliminated owing to errors of method (p. 39). In the diagrams squares represent patients from the old series and circles patients from the new series.

### DISTRIBUTION OF PULMONARY BLOOD VOLUMES

For patients subjected to duplicate *PBV* determinations at rest, the mean of these volumes was calculated. The distribution of pulmonary blood volumes has been plotted in Fig. 11 and Table 7 presents means and ranges for *PBI*, *PBI* per square metre *BSA* and per metre stature, stature, weight and body surface area.

*Comment.* The largest single group in both series comprised patients with *PBI* between 550 and 599 ml. The means and ranges for these subgroups were also closely similar. Owing to a slight preponderance of small *PBV*'s in the old series, its mean *PBI* was 15 ml lower than that for the new series.

The age and sex distributions of the old and new series do not differ appreciably. The patients in both series with few ex-



11 *PBI* distributions in the old (open columns) and the new (hatched columns) series.

ceptions had cardiovascular diseases associated with a tendency to pulmonary venous pressure elevation with increasing severity of the disease. The most common diagnosis was mitral stenosis. The compositions of the two series nevertheless deviated in some respects. In the old series 16 patients (48%) belonged to functional groups III–IV as against 9 patients (25%) belonging to group III and none to group IV in the new series. The mean pulmonary arterial pressure exceeded 30 mm Hg in 8 patients (24%) from the old series and in 6 patients (17%) from the new series. Mean left atrial pressures over 15 mm Hg were observed in

Table 7 Mean and ranges for  $PBF$ ,  $PBF$  per square metre body surface,  $PBF$  per litre of lung (weight) and as well as for stature, weight and body surface.

|             | No. of patient | $PBF$ ml      | $PBF$ m <sup>2</sup> $PBF$ l | $PBF$ / m Height ml m | Height cm     | Weight kg  | Surface area m   |
|-------------|----------------|---------------|------------------------------|-----------------------|---------------|------------|------------------|
| Old series  | 33             | 348 (187-722) | 311 (156-461)                | 323 (121-476)         | 169 (124-185) | 65 (48-73) | 1.76 (1.42-2.07) |
| New series  | 28             | 604 (323-816) | 312 (106-469)                | 323 (106-492)         | 170 (124-183) | 66 (50-84) | 1.76 (1.48-2.16) |
| Both series | 61             | 577 (187-822) | 312 (106-469)                | 323 (121-492)         | 170 (124-183) | 65 (48-84) | 1.7 (1.42-2.16)  |

13 patients (39%) from the old series and in 10 patients (28%) from the new series. Pulmonary vascular resistances exceeding 2 Units were encountered in 14 patients (42%) in the old series and in 9 patients (32%) in the new series. The old series included three patients with chronic obstructive pulmonary disease versus nil in the new series. These data suggest that abnormalities of the pulmonary vessels were more frequent in the old series than in the new and that might in turn contribute to the slightly dissimilar  $PBF$  distributions in the two series. Among the five patients in the old series with  $PBF$  around 300 ml or less (Nos. 10, 15, 23, 25, 31) four were either in functional group IV with chronic heart failure (Nos. 10 and 25) or had chronic obstructive pulmonary disease combined with mitral stenosis (Nos. 23 and 31).

Data from previous reports on the use of the double indicator technique in man have been collected in Table 8. The data published by McGARRY *et al.* (86) supplemented the findings of MILLER *et al.* (90). Initially published in 1955 in Japanese, LUCIEN *et al.* (75) was later (1960) reissued in English by FUJIMOTO *et al.* (48). DOCK *et al.* (26) corrected the hematocrit for trapped plasma, unlike McGARRY *et al.* and the present author. Other papers in the table do not specify what was done about the hematocrit. However, as noted elsewhere (p. 38) correction for trapped plasma negligibly influences the  $PBF$ .

The series in the table were without exception composed of patients all or most of whom had left heart diseases. Like the present investigation, the series of McGARRY *et al.*, DOCK *et al.* and OAKLEY *et al.* included patients representing vari-

Table 8. Reported results of *PBF* estimations by the double indicator technique.

| Authors                              | No. of patients | <i>PBF</i> /m <sup>2</sup> <i>BSA</i> |         | Indicators                                  |
|--------------------------------------|-----------------|---------------------------------------|---------|---|
|                                      |                 | Mean                                  | Range   |   |
| KURITA 1953                          | 3               | 373                                   | 263-487 | T 1834 1½ times                             |
| MILNOR, JONES <i>et al.</i> 1960     | 19              | 363                                   | 126-598 | OG two times                                |
| MCGARY ROVETT <i>et al.</i> 1963     | 42              | 309                                   | no data | OG two times                                |
| FERROSO ARACHIDIA <i>et al.</i> 1961 | 11              | 462                                   | 283-642 | T 1824 two times                            |
| DOCK, KRAUS <i>et al.</i> 1961       | 48              | 32*                                   | 17*-634 | T 1824 and <sup>125</sup> I-albumin simult. |
| OAKLEY GLICK <i>et al.</i> 1962      | 44              | 343                                   | 12.-453 | OG two times                                |
| Present study both materials         | 69              | 328                                   | 1.8-469 | BSP and OG simult.                          |

ous stages of heart failure as well as patients with normal or nearly normal haemodynamics. The mean *PBF* in these four series lies around 300 ml per square metre *BSA* and the respective ranges are similar. If the upper extreme value in DOCK *et al.*'s series is excluded the composite *PBF* range becomes 172-527 ml per square metre *BSA*.

The *PBF* means in the series of KURITA, MILNOR *et al.* and FERROSO *et al.* (38, 75, 90) are somewhat higher than in the other series, but the differences between the means and ranges are no larger than they probably could be accounted for by random variations in the status of the patients composing the various series. The small series of FERROSO *et al.* was composed exclusively of patients with mitral stenosis, the large majority of whom (9 of 11) had very high left atrial pressure.

*PBF* has also been determined with the aid of quantitative radiocardiography. Thus LEWIS *et al.* (80) reported that 18 patients without cardiovascular disease had a mean *PBF* of 548 ml with a range of 323 to 721 ml, corresponding to 312 ml per square metre *BSA* with a range from 211 to 403 ml per square metre *BSA*.

Eight patients who had cardiovascular disease exhibited a *PBF* range from about 400 to 760 ml. The same group of workers have later developed the radio-cardiographic method further as reported by GRISTINI *et al.* (61). In 17 men without cardiovascular affections they found that the *PBF* ranged from 318 to 694 ml and averaged 519 ml, corresponding to a range from 208 to 373 ml per square metre *BSA* and a mean of 293 ml per square metre *BSA*. In seven patients with various types of heart disease in most cases involving the left heart the *PBF* varied between 370 and 1037 ml, corresponding to 248 to 540 ml per square metre *BSA*. These results are well compatible with those obtained by the double indicator procedure.

#### CLASSIFICATION OF PATIENTS BY DEGREE OF DISEASE

To obtain a group of patients with minimal haemodynamic abnormalities, the following criteria were adopted:

- I Functional group I or II.
- \* Sinus rhythm.

- 3 Systolic pulmonary arterial pressure not exceeding 30 mm Hg and mean left atrial pressure not exceeding 13 mm Hg at rest.
- 4 Normal vascular pattern in lungs as revealed by roentgenograms exposed before PBI determination. (An experienced roentgenologist sorted films for patients satisfying criteria 1 to 3 into groups with normal and abnormal vascular patterns.)

These four criteria were met by altogether 20 patients: 11 from the old and 9 from the new series. These patients constitute what will henceforth be known as Group A and the remainder what will be called Group B.

The patients in Group A included Nos. 6, 7, 8, 14, 16, 18, 21, 22, 27, 28 and 32 from the old series and Nos. 41, 50, 54, 58, 63, 66, 70, 71 and 72 from the new series. Nine were women and 11 men, their ages ranged from 17 to 49 years and averaged 30 years. The diagnoses were:

|   |    |
|---|----|
| Mitral stenosis combined with aortic valvular disease             |    |
| Mild mitral regurgitation   | 1  |
| Subaortic stenosis, aortic valvular disease or aortic coarctation | 13 |
| Coronaryopathy  | 1  |
| Paroxysmal tachycardia  | 1  |
| Normal haemodynamics without signs of cardiovascular disease      |    |

The mean cardiac output was 5.0 litres per minute corresponding to 2.5 litres per square metre BSA. The mean pulmonary arterial pressure averaged 14 mm Hg and ranged from 8 to 21 mm Hg. The mean left atrial pressure averaged

6 mm Hg and ranged from 2 to 13 mm Hg. Ten of the patients in Group A (Nos. 8, 14, 16, 18, 21, 27, 28, 32, 50, 66) were also examined during light exercise (160–300 kpm/min) obtained by working an electrically braked bicycle ergometer in the supine position. This caused only one of them (No. 8) to show an abnormal rise in left atrial pressure while the corresponding pressure in the others remained unchanged or fell slightly.

The patients in Group B satisfied either none or up to three of the four criteria. Group B comprised 40 patients: 22 from the old series and 27 from the new series. Varying from 8 to 63 mm Hg, their mean pulmonary arterial pressure averaged 20 mm Hg. The mean left atrial pressure varied between 0 and 41 mm Hg and averaged 16 mm Hg. The left atrial pressure at rest was 13 mm Hg or lower in 22 of the patients in Group B. Six of the latter (Nos. 30, 36, 39, 51, 60, 68) were exercised, which caused the left atrial pressure to rise excessively in all of them except No. 39 who had pulmonary stenosis.

**Comment.** The patients in Group A were by definition free from cardiovascular symptoms at rest. Their mean pulmonary arterial and left atrial pressures agreed closely with those HARRIS & HEATH (57) specified for normal pressures in the pulmonary artery ( $\bar{P} = 14 \pm 3$  mm Hg) and in the PCF position  $\bar{P}_{PCF} = 9 \pm 3$  mm Hg). The upper limit of the mean pulmonary arterial and left atrial pressures in Group A fell within the range of plus two standard deviations of pressure in the pulmonary artery ( $+2 \pm 3$  mm Hg) and in the PCF position ( $+2 \pm 3$  mm Hg) according to HARRIS & HEATH. BARRATT, BOYES &

Wood (7) measured the pressure in the pulmonary artery at rest 76 times in 24 normal subjects and in the PCV position 38 times in 21 normal subjects. The mean pressure in the pulmonary artery varied between 10 and 22 mm Hg (average 17 mm Hg) and that in the PCV position between 8 and 15 mm Hg (average 13 mm Hg). According to a WHO Expert Committee on Chronic Cor Pulmonale (144) pulmonary hypertension may be considered present when the mean pressure in the pulmonary artery exceeds 25 mm Hg at rest. In Group A the highest mean pressure in the pulmonary artery at rest was 21 mm Hg.

Our knowledge of pressure variations in the left atrium of normal man is sketchy. BRAUNWALD *et al* (15) reported that the pressure in the left atrium of 18 patients without cardiovascular disease varied from 0 to 12 mm Hg at rest which agrees well with the assumption that the upper limit of normal variation is about 13 mm Hg.

The mean cardiac index in Group A fell in the upper range of normal means recorded in the supine position at rest by various laboratories and collated by WADE & BIANOR (138). The mean cardiac index in the supine position at rest was 6 litres per minute for 11 adult normals of both sexes observed in the laboratory where the present investigation was carried out (84). This figure is somewhat lower than that for Group A. The haemodynamic reaction during the exercise test undergone by half the patients in Group A was additional evidence that abnormal pulmonary vascular changes were of minor importance in Group A.

With the possible exception of Nos. 14

and 16 who had murmurs regarded as innocent the patients in Group A were not normal. Most of them had diseases affecting the left side of the heart but in view of the criteria for their selection and their haemodynamic data their pulmonary haemodynamics, including pulmonary blood volume presumably deviated little from normal at rest.

The patient in Group B had two things in common. None of them satisfied all the four criteria for Group A and all of them except No. 39 had diseases affecting the left side of the heart which in advanced stages tend to cause pulmonary venous hypertension. All functional groups from I to IV were represented. Some of these patients had sinus rhythm and others had arrhythmia. The pressures in the pulmonary artery and in the left atrium varied from normal to markedly excessive. Evidently therefore Group B was composed of heterogeneous patients with varying degrees of disease and the demarcation from Group A was probably diffuse. However even if Groups A and B did overlap it is evident that the patients in Group B on the whole had more advanced diseases than those in Group A. Hence vascular abnormalities in the lungs were more common and more pronounced in Group B than in Group A.

Nobody has yet reported the results of PBI determinations with the aid of the double indicator technique in a series of normal subjects, no doubt owing to the complexity and somewhat drastic nature of the procedures involved. Against this background the object of classifying the patients in the present investigation as described in the foregoing was—on the basis of results in Group A and compari-

alone with other studies in animals and man—to predict what one should expect to find in normal subjects and, by contrasting Groups A and B to establish how cardiovascular diseases of increasing severity may influence the pulmonary blood volume

## PULMONARY BLOOD VOLUME AND BODY SIZE

For those patients in whom duplicate  $PBV$  determinations had been made the mean was used in the calculations discussed here. Relations between  $PBV$  and, respectively stature, body weight and body surface area in Groups A and B as well as in the new and old series, separately and combined, are set out in Table 9.  $PBV$  has been plotted against  $BSA$  in Fig. 12. The equation for the regression

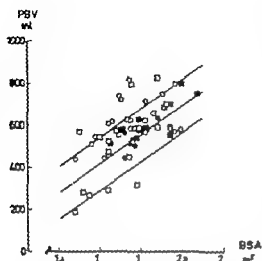
of pulmonary blood volume upon body surface area in Group A was  $PBV = 687 BSA - 683$ . This regression line has an intercept on the abscissa corresponding to  $BSA = 0.88$  square metres.

*Comment.* Suppose the double indicator procedure provides a correct estimate of the true pulmonary blood volume, one would expect to find a positive correlation between  $PBV$  and body size in normals. Haemodynamic and vascular abnormalities in the lungs would modify such an association. But since the degree and nature of abnormal deviations in pulmonary blood volume are most unlikely to be dependent on body size, a similar positive correlation may exist also in sufficiently large series of patients with cardiovascular disease.

In the old series as well as in the new series,  $PBV$  was significantly correlated

Table 9. Correlations between  $PBV$  and body size measures (stature, weight and surface area). ( ) denotes that the coefficient of correlation or the difference between two such coefficients is significant.

| Correlated factors     |  | Correl. coeff.<br>Group A | Correl. coeff.<br>Group B | Difference<br>$A - B$ | Correl. coeff.<br>Group A + B |
|------------------------|--|---------------------------|---------------------------|-----------------------|-------------------------------|
| Old series             |  | 11 patients               | 22 patients               |                       | 33 patients                   |
| $PBV$ and height       |  | 0.75 ( )                  | 0.31 ( )                  | +0.24                 | 0.53 ( )                      |
| $PBV$ and weight       |  | 0.67 ( )                  | 0.64 ( )                  | +0.03                 | 0.65 ( )                      |
| $PBV$ and surface area |  | 0.74 ( )                  | 0.8 ( )                   | +0.1                  | 0.72 ( )                      |
| New series             |  | 9 patients                | 47 patients               |                       | 56 patients                   |
| $PBV$ and height       |  | 0. ( )                    | 0.43 ( )                  | +0.43 ( )             | 0.4 ( )                       |
| $PBV$ and weight       |  | 0.5                       | 0.1                       | +0.                   | 0.3                           |
| $PBV$ and surface area |  | 0. ( )                    | 0                         | -0.32 ( )             | 0.8 ( )                       |
| Both series            |  | 20 patients               | 69 patients               |                       | 89 patients                   |
| $PBV$ and height       |  | 0.91 ( )                  | 0.40 ( )                  | +0.3 ( )              | 0.53 ( )                      |
| $PBV$ and weight       |  | 0.8 ( )                   | 0.42 ( )                  | +0.2                  | 0.61 ( )                      |
| $PBV$ and surface area |  | 0.8 ( )                   | 0.8 ( )                   | +0.4 ( )              | 0.83 ( )                      |



12 PBV plotted against body surface area (BSA) in the old (squares) and the new (circles) series, filled symbols representing Group A and open symbols Group B. The regression line for Group A ( $PBV = 887BSA - 523$ ) and lines for  $\pm 2$  residual standard deviations are shown.

to stature, weight and BSA. The corresponding correlations were as expected, stronger in Group A than in Group B, the differences with respect to stature and BSA being significant in the new series and in the combined old and new series. Stature and BSA were equivalent and superior to weight as predictors of PBV.

It was decided to discuss the results in terms of relations between PBV and BSA in order to facilitate comparison with the large majority of other studies which are based on BSA. Otherwise stature would perhaps have been preferable because the results would have been essentially similar and unlike BSA it can readily be measured directly. In the present investigation BSA was found with the aid of DuBois' formula. Although this formula has been criticized for being based on too few

direct measurements, more recent studies show that DuBois' formula applied to adults is no more inaccurate than others based on much more data (118).

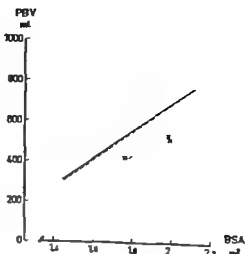
Correlations between estimates of body size and other physiological entities reflect the simple fact that organs and organ functions often are quantitatively larger in big persons than in small. However, neither stature nor weight or body surface area is always an ideal estimate for comparing physiological data from different patients because of individual variations in body build and in the proportions of muscles and fat. The strong correlation between pulmonary blood volume and body size in the present investigation was probably caused by the fact that the majority of patients were of fairly average build and obesity was uncommon. A concept independent of individual fat mass variations and referring to a more uniformly composed body fraction than total body mass, the so-called lean body mass (9, 31) would perhaps—as in the case of red cell mass (33)—be the best body size estimate for predicting pulmonary blood volume.

When a positive correlation exists between an observed physiological factor and body size and data from patients of different sizes are to be compared, a common practice is to express results in terms of the ratio of the observed value to some body size estimate such as stature, weight or surface area. This is permissible provided the observed factor is an approximately linear function of the body size estimate within the range of variation under study and the line describing the regression of the observed factor upon body size passes through the origin, that

is its equation must have the form  $y = bx$ . Unless these two conditions are satisfied, erroneous conclusions may be drawn when ratios are used uncritically for comparing individual patients or groups of patients with dissimilar body size distributions. These basic questions have been discussed in general form by TANZLER and by AXERVALL & CARLSTRÖM (1 130 131)

All who have used the double indicator method have expressed the results as pulmonary blood volume per body surface area, even DOCK *et al* (5) who studied but found no association between *PBV* and *BSA* perhaps because their patients in general had diseases in a more advanced stage than the patients in the present investigation. Such an assumption is borne out by findings for the four patients with normal haemodynamics in the series of DOCK *et al*. Three patients have been plotted in Fig 13. The positions of the points suggest a strong correlation between *PBV* and *BSA* and the regression line inserted by hand does not deviate appreciably from the corresponding line for Group A.

With the aid of quantitative radio-cardiography LEWIS *et al* (80) found a positive but not significant correlation ( $r = 0.36$ ;  $p > 0.1$ ) between *PBV* and *BSA* in 18 haemodynamically normal patients. Later however the same team (81) reported the results of *PBV* determinations by a slightly modified technique. Now a group of 17 men without cardiovascular disease was studied. The age of 16 patients was between 24 and 50 years and one was 74. There was a strong and significant correlation between *PBV* and *BSA* and the coefficient of correlation was  $+0.84$ .



13. Association between *PBV* and body surface area. The solid line is the regression line for Group A (cf Fig 12). The broken line close to it is the corresponding regression line ( $PBV = 688BSA - 708$ ) obtained by LEWIS *et al*. The broken line lower down is the corresponding regression line estimated by the writer for four haemodynamically normal subjects studied by DOCK *et al*.

the same value as that for Group A. Moreover the equation of the regression line  $PBV = 688BSA - 708$  was practically identical to that for Group A (Fig 13). Like Group A their patients without cardiovascular disease were not strictly speaking normal subjects but the *PBV* changes could be assumed to deviate little from normal.

According to the results of various investigations the line describing regression of *PBV* upon *BSA* deviates considerably from the form  $y = bx$  under approximately normal conditions. The three regression lines in Fig 13 all cross the abscissa at around 1 m *BSA*. Consequently it is wrong to use the ratio  $PBV/m^2$  *BSA* for comparing patients of different sizes.

Since *PBV* is a fraction of the total



blood volume ( $TBI$ ) the two are very probably closely associated under normal conditions. In addition to  $PBI$  GRUTTINI *et al* (51) determined  $TBI$  with the aid of a radioactive plasma indicator ( $RISA$ ). In patients without cardiovascular abnormalities  $PBI$  and  $TBI$  were strongly correlated ( $r = +0.81$ ) and despite large  $PBF$  variations with body size differences, the ratio was constantly around 0.10 (mean ratio = 0.100 standard deviation = 0.013). This may be accounted for by the fact that  $TBI$  is associated with body size in the same way as  $PBF$  (16). Accordingly the influence of body size upon  $PBF$  can be eliminated by expressing  $PBF$  as a fraction of  $TBI$ .

## PULMONARY BLOOD VOLUME UNDER PRESUMED NORMAL AND ABNORMAL CONDITIONS

### Group A

The patients in Group A had  $PBF$ 's ranging from 333 to 795 and averaging 554 ml. Their  $BSA$  varied between 1.43 and 2.0 and averaged 1.90  $m^2$ . A  $BSA$  of 1.73  $m^2$  — a commonly accepted mean  $BSA$  for adults — inserted into the regression equation  $PBI = 687BSA - 683$  yields  $PBI = 506$  ml the mean expected at 1.73  $m^2$   $BSA$ . The correction was made to facilitate comparison with other studies of pulmonary blood volume. Age and sex had no manifest association with  $PBI$  in Group A.

**Comment.** On the sketched regression line (Fig. 13) for DOCK *et al* a four patients with normal circulatory dynamics (25)  $BSA = 1.73$   $m^2$  corresponds to  $PBI$  about 400 ml. McCLAVE *et al* (86) series

included five haemodynamically normal patients for whom unfortunately separate laboratory data were not specified. For these patients the mean relative  $PBI$  was 230 ml/ $m^2$  and the mean ratio of  $PBI$  to predicted  $TBI$  was 0.09.

The radiocardiographically estimated  $PBI$  of LEWIS *et al* (80) 18 patients without cardiovascular disease ranged from 323 to 721 and averaged 546 ml. And for the 17 similar patients studied by GRUTTINI *et al* (51) the  $PBI$  ranged between 318 and 694 ml with a mean of 519 ml corresponding to 293 ml/ $m^2$ .  $BSA$  varied from 1.53 to 1.98  $m^2$ . The relation between  $PBI$  and  $BSA$  was practically identical to that in Group A and solution of the regression equation published by the latter workers for  $BSA = 1.73$   $m^2$  yields  $PBI = 500$  ml (Fig. 13).

LAURILOF *et al* (76) calculated the  $PBI$  of seven normal subjects by deducting from the measured central blood volume its estimated extrapulmonary portion the resulting mean  $PBI$  being 963 ml. The reason for this high value might have been the fundamental difficulties of anatomically demarcating the central blood volume (83, 147).

BACKMANN (4) measured the pulmonary blood volume postmortally in 7 adults with normal lungs. The mean  $PBF$  of one lung (4 left and 3 right lungs according to the author's personal communication) was 269 ml and the range 1.8 to 307 ml. Doubling these values yields a  $PBI$  mean of 518 ml and a range of 356 to 724 ml. The latter figures agree closely with those of the present author LEWIS *et al* and GRUTTINI *et al* and constitute additional evidence for the absence normally of non-circulating blood pools in the lungs.

As long ago as 1904 PLUMMER (107) suddenly ligated the vessels to and from the lungs in spontaneously breathing anaesthetized dogs and then measured the amount of blood in the lungs. The mean  $PBF/TBF$  ratio was 0.11 in inspiration and 0.09 in expiration. Previously in 1889 HENCK & SPENGLER (62) by similar experiments on rabbits had found that the  $PBF/TBF$  ratio fluctuated between 0.08 and 0.10. In 1961 PARRISH *et al.* (102) estimated the  $PBF$  of dogs by injecting a radioactive indicator into a jugular vein and simultaneously collecting blood in the pulmonary artery and left atrium followed by analogue-computer analysis of the dilution curves. The mean  $PBF/TBF$  ratio for 31 estimations in 18 dogs was 0.117.

Reports from various laboratories suggest that in normal adult the mean  $PBF$  is of the order of 0.5 litres and, owing to body size differences, the range of variation is approximately 0.3 to 0.8 litres. The mean value of 0.5 litres corresponds to about 10 per cent of the total blood volume which agrees well with the relative proportion of  $TBF$  found in studies in man (51) and animals (62, 103, 107). In this context it may be emphasized that one should not be misled by papers where the concept  $PBF$  is discussed in terms of observed blood volumes which, in addition to  $PBF$ , included blood in the left heart, in systemic arteries and sometimes also blood in the right heart and venous vessels (77, 108, 110).

The problem whether age and sex are in any way associated with  $PBF$  must await future investigation on series considerably larger than that available to the writer. It would be valuable if  $PBF$

could be determined by the double indicator procedure in series of subjects who satisfy requirements of normalness better than in the present study but complexity of the procedures renders difficult the attainment of this aim.

The present investigation provided no information on how the blood in the lungs is distributed among the various components of the pulmonary vascular bed. A rough idea can nevertheless be obtained from certain investigations on animals and man, assuming that the proportions of  $PBF$  in corresponding parts of the pulmonary vascular bed are similar in dogs and man. According to von HAYEK (61) the capacity of the pulmonary arteries up to the hill of the lungs is some 50 ml in man *post mortem*, consequently about 10 per cent of  $PBF$ . FRANK, BOYD & DuBOIS (37) found that the blood volume in the whole pulmonary arterial system of anaesthetized dogs averaged about 30 per cent of  $PBF$  corresponding to some 150 ml in a human with a  $PBF$  of 0.5 litres. From measurements of the pulmonary diffusing capacity in man the pulmonary capillary volume has been estimated to about 90 ml (40, 41) or about 20 per cent of  $PBF$ . This would leave altogether 50 per cent of  $PBF$  or on average some 250 ml for the pulmonary veins, suggesting that these comprise the largest blood reservoir in the lungs.

#### Group B

In Fig. 1, page 46,  $PBF$  has been plotted against  $BSA$  for all the 60 patients in the new and old series. The three lines are the regression line for Group A

( $PBI = 687BSA - 693$ ) and on each side of it the lines for plus and minus two residual standard deviations ( $RSD$ ). According to the classification described elsewhere (p 42) 20 of the 69 patients belonged to Group A and the other 49 to Group B.  $PBI$  for 30 of the patients in Group B the majority fell within the range of  $\pm 2RSD$  for Group A, while 16 of the remaining 19 fell above  $+2RSD$  and only 3 below  $-2RSD$ . This means that there was among the patients in Group B a stronger tendency to have increased  $PBI$  than decreased by comparison with Group A as is also expressed by the fact that 37 of the patients in Group B lie above the line of regression but only 1\* below it. None of the 16 patients whose  $PBI$  deviated more than  $+2RSD$  above the regression line for Group A were in functional group IV or had chronic obstructive pulmonary disease. The latter two categories included altogether 9 patients all from the old series. The three patients deviating more than  $-2RSD$  below the regression line for Group A were either in functional group IV or had chronic obstructive pulmonary disease. In addition to obstructive pulmonary disease two of them (Nos 23 and 31) had mitral stenosis and the third (No 25) was in functional group IV in an advanced stage of mitral stenosis. Thus, compared with Group A, those patients in Group B with chronic obstructive pulmonary disease or who were in functional group IV either had unchanged or reduced  $PBI$  while the remainder either had unchanged or increased  $PBI$ .

*Comment.* With one exception the patients in Group B had diseases involving the left side of the heart and 27 of the 49

patients had elevated left atrial pressure at rest ( $P_{LA} > 13$  mm Hg). Six of the 22 without left atrial hypertension at rest were exercised the 5 who had left heart disease developing elevated left atrial pressure during exercise.

Pulmonary vascular changes associated with left heart disease are due to the development of left atrial and pulmonary venous hypertension leading to pulmonary arterial hypertension. The  $PBI$  alterations observed in Group B must be discussed against the background of our present knowledge about the pathology and anatomy of the pulmonary vascular bed in left heart disease. Summarizing surveys, in all essentials, unanimous of this subject have been published in the past few years by HARRISON (60), HARRIS & HEATH (58) and SPENCER (128). The earliest histological changes in conditions attended by abnormal pulmonary venous pressure rise take the form of capillary dilatation. In chronic pulmonary venous hypertension muscular hypertrophy develops on the arterial and venous sides; in due course the major pulmonary arteries become dilated while the distal portions of the elastic arteries, the muscular arteries and the arterioles become narrowed and in far advanced stages fibrinoid endothelial deposits in the small arteries, atheromatosis and thromboembolism often contribute further to the vascular obstruction. The pulmonary lymphatics are also dilated in diseases with chronic pulmonary venous hypertension. The interstitial and alveolar oedema is in due course organized into fibrous tissue leading to destruction of alveoli and vessels at the same time as the remaining capillaries

exhibit everything from obstruction to dilatation. PARKER & WILKS (101) maintained that capillary dilatation was absent in cases of combined pulmonary emphysema and advanced mitral stenosis. In conditions with chronic pulmonary venous hypertension the pulmonary changes are more pronounced in the caudal than in the cranial parts of the lungs but they are basically similar irrespective of what causes the pulmonary venous hypertension (125-128). Mitral stenosis is the disease which tends to lead to the most advanced pulmonary changes, probably because its course often is protracted.

JAMES OWEN & THOMAS (69) studied the capacity of the smallest pulmonary arteries ( $^{\circ}$  mm to  $30\ \mu$  in diameter) in various disorders. They found that the capacity of these vessels was subnormal in emphysema, left heart failure, mitral valvular disease and pulmonary hypertension.

These facts indicate that pulmonary venous hypertension is associated with changes some of which tend to increase and others to decrease the amount of blood in the lungs. BACKMANN (4) quantitatively estimated the *PBI* at autopsy of healthy and diseased human lungs. He contentedly stated *PBI* per lung, right or left. For 7 lungs classified as normal the *PBI* per lung ranged from 178 to 307 and averaged 230 ml; the corresponding figures for 7 lungs with senile or obstructive emphysema being 123 to 157 and 14 ml. Accordingly the highest *PBI* among the abnormal lungs was smaller than the lowest *PBI* among the normal lungs. Furthermore for 5 lungs from patient with emphysema and left heart failure the mean *PBI* per lung was 276 ml and the

range 182 to 406 ml. Here no *PBI* was smaller than the highest *PBI* for patients with emphysema only, suggesting that *PBI*-reducing factors (emphysema) compete with *PBI*-increasing factors (left heart failure). Whereas very high total *PBI*'s were noted in a patient with mitral stenosis not accompanied by pulmonary fibrosis (633 ml) and another who died of acute left heart failure (452 ml) the *PBI*'s of two patients with mitral valvular disease and pulmonary fibrosis were considerably smaller (224 and 178 ml).

Experiments in dogs by LINDSEY & GUTTORF (83) suggest that a sharp increase in *PBI* accompanies acute left heart failure induced by aortic constriction.

The hypothesis outlined in the following was made concerning the presumed association *in vivo* between the capacity of the pulmonary vascular bed and the course of left heart disease. In the early stages of diseases with pulmonary venous hypertension volume increasing factors dominate because the pressure rise in the lungs happens in an intact vascular bed with comparatively high compliance of capillaries and veins, where the increase in volume probably would be greatest. In chronic pulmonary venous hypertension secondary changes in the pulmonary vessels become more pronounced with rising degrees of disease leading to reduced vascular compliance simultaneously with accentuation of obliterative vascular lesions. These factors inhibit the volume increasing action of pressure elevation in the lungs on the pulmonary capillaries and veins. The presence of pulmonary emphysema is a factor that reduces the capacity of the

pulmonary vascular bed. Among patients with left heart disease of varying degrees and durations who also have emphysema one would expect the capacity of the pulmonary vascular bed to be normal, supernormal or subnormal depending on how pressure vascular compliance and obliterative vascular lesions are distributed in individual patients. During the course of diseases with chronic pulmonary venous hypertension the capacity of the pulmonary vascular bed would probably be greater than normal at first but in due course when the volume reducing factors have become sufficiently pronounced, it would contract once more. Another potentially *PBF* reducing mechanism should be considered in patients with excessive cardiac enlargement. The expanded heart volume could then encroach upon the available intrathoracic space and compress the lungs.

The composition of Group B in the present investigation was heterogeneous and permitted no detailed analysis of the results. *PBF* varied from smaller than to greater than in Group A in which *PBF* was presumed approximately normal. The volume increasing factors were dominant in Group II which could be in accord with the fact that judging by their clinical data, most of the patients were not in a particularly advanced stage of their disease.

All but two (Nos. 2 and 39) of the 16 patients whose *PBF* was above  $+2\text{RSD}$  in Fig. 1\* had left atrial pressures exceeding 13 mm Hg either at rest or during exercise suggesting that pulmonary venous hypertension is a *PBF* increasing factor. Patient \* who was not exercised

belonged to functional group II and had combined mitral and aortic valvular disease. X-ray examination disclosed accentuation of the pulmonary vascular pattern and gross cardiac enlargement (680 ml/ $\text{m}^2$ ). Angiography revealed pronounced dilatation of the left ventricle and left atrium the estimated volume of the latter being a bit over 200 ml, probably a consequence of excessive left atrial pressure during exercise. In Patient 39 who had pulmonary valvular stenosis, there was also a very pronounced, poststenotic dilatation of the pulmonary artery a fact which could account for the comparatively large *PBF*.

All patients who were in functional group IV or had obstructive pulmonary disease belonged to the old series. None of them had significantly higher but some had significantly lower *PBF* than the mean for Group A from which it may be inferred that the *PBF* reducing factors were prominent and sometimes dominant. In those with obstructive pulmonary disease emphysema was probably present as a *PBF* reducing factor. All in functional group IV had chronic heart failure and all but No. 11 had pulmonary vascular resistance in excess of 9 Units. Patient 11 was the only one with constrictive pericarditis the pressure in the right atrium was 15 mm Hg the same as in the left atrium. The cardiac volume index averaged 734 ml/ $\text{m}^2$  (range 500–1030) for the six patients in functional group IV and 5.5 ml/m for the other patients from the old series in Group B. The considerably larger cardiac volume in the patients in functional group IV might have constituted a further factor

tending to reduce pulmonary blood volume

In cases of cardiovascular disease combined with low blood flow and pulmonary vascular changes one might speculate that the lungs could contain pools of stagnant blood which would not be included in the  $PBI$  determined by the indicator dilution procedure but proof of such a mechanism remains to be found. The presence of stagnant blood in the lungs would tend to reduce the circulating pulmonary blood volume

If the left atrial indicator was mixed with only part of the blood in the atrium while the pulmonary arterial indicator was mixed with all the blood in the left atrium, the  $PBI$  determination would theoretically include some of the blood in the atrium. Conversely if both indicators were mixed to the same extent with the blood in the left atrium, the  $PBI$  determination would be correct. It is impossible to tell whether the former alternative could have had any quantitative significance in Group B and contributed to the tendency towards increased  $PBI$ . Many patients in Group B had pronounced enlargement of the left atrium but it did not seem the rule that the largest atria were accompanied by the relatively largest  $PBI$ . On the assumption that the  $PBI$  determinations reflect the capacity of the pulmonary vascular bed the results in Group B seem plausible. In view of the changes one would expect

LEWIS *et al* (40) used quantitative radiocardiography for  $PBI$  estimation in 17 patients with pulmonary emphysema 11 of them having pulmonary blood volumes less than the mean  $PBI$  for a group of patients without cardiovascular

disease. In a later publication from the same laboratory by GUSTINI *et al* (51) the mean  $PBI$  for 7 patients with emphysema was 454 ml compared with 519 ml for 17 patients without cardiovascular disease.

All workers who have used the double indicator procedure for  $PBI$  determination had series in which the majority or all of the patient suffered from some form of left heart disease. OAKLEY *et al* (50) divided patients with mitral valvular disease into three groups: those with mild, moderate and severe disease without specifying any criteria applied. But there were no differences in mean  $PBI/m^2BSA$  between the groups. McGARRY *et al* (86) compared  $PBI/m^2BSA$  in patients with minimal mitral stenosis and with moderate to severe mitral stenosis. The mean in the former group was similar to that for the five haemodynamically normal subjects but it was lower than the mean for the group with more marked disease. When all patients with mitral valvular disease were considered, the  $PBI/m^2BSA$  tended to be either unchanged or increased by comparison with the haemodynamically normal subjects.

### PULMONARY BLOOD VOLUME PRESSURES AND VASCULAR RESISTANCE IN THE PUL- MONARY CIRCULATION

Analysis of the association between  $PBI$  and the blood pressures in the pulmonary artery and left atrium must make allowance for the significant correlation between body size and  $PBI$ . To do this the first  $PBI$  determined for each patient was plotted against  $BSA$ . Then each

point was displaced along an imaginary line paralleling the line of regression for Group A to a point having the arbitrarily selected *BSA* value of  $1.8 \text{ m}^2$ . The *PBV* values corresponding to all these new points were estimated graphically and used as *PBI* values corrected for *BSA* in evaluation of the relations to blood pressures.

There was no association between *PBV* and mean pulmonary arterial pressure in the old series. Nor was there any obvious association in the new series between *PBI* and mean pulmonary arterial pressure levels not exceeding 20 mm Hg, but the mean *PBV* for those with pressures over 20 mm Hg (686 ml, standard deviation = 114 ml) was higher ( $p < 0.05$ ) than the mean *PBV* for those with lower pressures (600 ml, standard deviation = 108 ml).

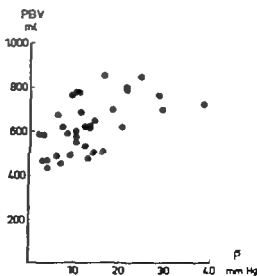
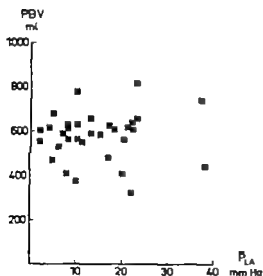
No association appeared in the old series (Fig. 14) between *PBI* and the mean left atrial pressure. Nor was there any obvious association in the new series

(Fig. 14) between *PBI* and mean left atrial pressure at levels not exceeding 13 mm Hg, but the mean *PBV* for those with pressures over 13 mm Hg (693 ml, standard deviation = 121 ml) was higher ( $p < 0.05$ ) than the mean *PBV* for those with lower pressures (586 ml, standard deviation = 102 ml).

Among the 33 patients in the old series the pulmonary vascular resistance (*PVR*) of 14 exceeded 2 Units and in 5 of these it was over 4 Units, the highest value being 10.5 Units. In the new series 8 of 36 patients had a *PVR* exceeding 2 Units and the *PVR* of only one of these exceeded 4 Units and was 8.9 Units.

Neither in the old series nor in the new series was there any obvious association between *BSA* corrected *PBV* and either *PVR* or pulmonary vascular pressure fall ( $P_{PA} - P_{LA}$ ).

*Comment.* Considering that few patients in the present investigation had appreciably elevated *PVR* it is natural that the



14 *PBV* corrected for body surface area plotted against mean left atrial pressure in the old (left diagram) and the new (right diagram) series.

pulmonary arterial pressure was similarly related to  $PBF$  as left atrial pressure. A discussion of the results will essentially be a repetition of arguments advanced in the foregoing.

The apparent anomaly that excessive left atrial pressure was associated with higher  $PBF$  than normal pressure in the new series but not in the old series could be accounted for by the fact that patients with excessive left atrial pressure in the old series were in a generally speaking more advanced stage of the disease than the corresponding patients in the new series, and the  $PBF$  increasing action of excessive pressure was therefore probably more prominent in the new series. When patient categories not represented in the new series — subjects in functional group IV or with obstructive pulmonary disease — had been excluded from the old series, the tendency in the latter became similar to that in the new series that  $PBF$  was on average higher at excessive than at normal pressure levels in the left atrium (535 and 588 ml, respectively).

Other workers have submitted similar explanations. Dock *et al* (25) found no association between  $PBF/m$  and left atrial pressure in their series as a whole but a significant positive correlation ( $p < 0.001$ ) when patients whose  $PFR$  exceeded 6.3 Units had been excluded, a circumstance they interpreted as evidence of more pronounced pulmonary vascular obstruction in patient with high  $PFR$ .

McGarry *et al* (80) sorted their 35 patient with mitral stenosis and 5 haemodynamically normal patient into one group with high and another with low  $PFR$ . A positive correlation between  $PBF/m^2$  and left atrial pressure existed

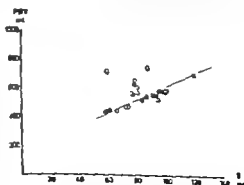
in both groups ( $p < 0.001$ ) but the high  $PFR$  group had smaller relative pulmonary blood volumes than the low  $PFR$  group.

As only three patients in the present study had  $PFR$  exceeding 8 Units no classification into groups with high and low  $PFR$  was possible besides estimation of normal or only slightly elevated  $PFR$  levels is highly inaccurate (58).

If  $PBF$  tends to rise in the early stages of disease with pulmonary venous hypertension but tends to fall during later stages the association between  $PBF$  and  $PFR$  ought theoretically to vary with the  $PFR$  level at which the association is studied.

## PULMONARY BLOOD VOLUME AND STROKE VOLUME

Associations between  $PBF$  and stroke volume ( $SV$ ) are illustrated in Fig 15. Only the first of duplicate  $PBF$  determinations was taken into account. Judging by the diagrams, a positive correlation



15.  $PBF$  plotted against stroke volume ( $SV$ ) in the old (squares) and the new (circles) series, filled symbols representing Group A and open symbols Group B. The regression line for Group A ( $PBF = 4.45 SV + 140$ ) is shown.



existed in both the old and the new series between  $PBI$  and stroke volume at  $SI$  levels above about 70 ml but they were not obviously associated below this level. In Group A a positive correlation was present between  $PBI$  and  $SI$  ( $r = 0.53$ ,  $p < 0.05$ ) and the regression line conformed to the equation  $PBI = 4.86 SI + 150$ . In Group A, too  $SI$  was positively correlated to  $BSA$  ( $r = 0.8$ ,  $p < 0.05$ ) the regression line having the equation  $SI = 115 BSA - 121$  (Fig. 16). In both the old and the new series patients belonging to Group B tended to have larger  $PBI$  than expected from the regression of  $PBI$  on  $SI$  in Group A.

**Comment.** The fact that no association between  $PBI$  and  $SI$  could be discerned at  $SI$  below about 70 ml implies that the normal association between  $PBI$  and  $SI$  is disturbed at subnormal  $SI$  levels, at least among patients such as those in the present investigation. The relation between  $PBI$  and  $SI$  in Group B was a consequence of the fact that many patients had reduced  $SI$  while the majority

had unchanged or increased  $PBI$  in relation to patients in Group A.

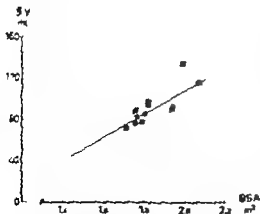
The positive correlation between  $PBI$  and  $SI$  in Group A need not be due to interaction as it can be fully accounted for by the fact that both factors normally are dependent upon body size. The results in Group A agree closely with those reported by GROSVENOR *et al.* (51) who among patients without cardiovascular disease found a positive correlation between  $PBI$  and  $SI$  ( $r = 0.88$ ,  $p < 0.001$ ) and their regression equation was  $PBI = 5.51 + \dots$

On good grounds it is prudent to use the concept "stroke volume index" ( $SI/m^2$ ) as cautiously as the pulmonary blood volume index ( $PBI/m^2$ ). JONES *et al.* (70) studied the association between  $SI$  and  $BSA$  in normal subjects. Judging by their diagram a regression line only for adult would intersect the abscissa far from the origin somewhere between  $BSA +1$  and  $+1.5 m^2$ . The corresponding line for Group A cuts the abscissa at  $BSA = 1.1 m^2$ . The use of the concept stroke volume index is based upon the premise that the regression line goes through the origin something there are grounds for doubting at least in adults.

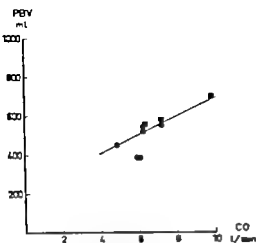
## PULMONARY BLOOD VOLUME, CARDIAC OUTPUT AND PULMONARY MEAN TRANSIT TIME

$PBI$  was computed as the product of  $CO$  and  $MTT_{pulm}$  and associations between these three factors were analyzed. Only the first of duplicate determinations was considered.

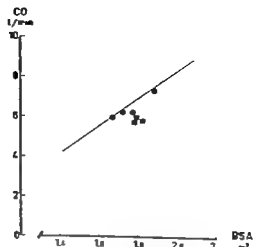
In Group A there was no association between  $CO$  and  $MTT_{pulm}$  nor between  $PBI$  and  $MTT_{pulm}$  but a positive correla-



16 Stroke volume plotted against body surface area in Group A. The regression line ( $SI = 115 BSA - 121$ ) is shown.



1 PBF plotted against cardiac output (CO) in Group A. The regression line ( $PBF = 45CO + 217$ ) is shown.



18 Cardiac output plotted against body surface area in Group A. The regression line ( $CO = 6.64BSA - 3.6$ ) is shown.

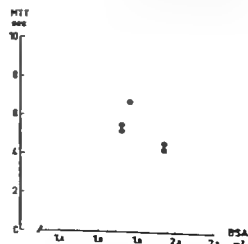
tion existed between PBF and CO (Fig. 1  $r = 0.45$ ,  $p < 0.05$  regression equation,  $PBF = 45CO + 217$ ) and also between CO and BSA (Fig. 18  $r = 0.86$ ,  $p < 0.05$  regression equation,  $CO = 6.64BSA - 3.6$ ). On the other hand,  $MTT_{pulm}$  was independent of BSA (Fig. 19  $r = 0.18$ ,  $p > 0.05$ ) and averaged 4.83 seconds with standard deviation = 0.86 seconds, corresponding to 18 per cent of the mean. Lastly, as demonstrated in the foregoing a significant positive correlation existed between PBF and BSA (Fig. 1 and Table 9).

In Figs. 20, 21 and 22 CO has been plotted against  $MTT_{pulm}$ , PBF against CO and PBF against  $MTT_{pulm}$  in the old series and in the new series.

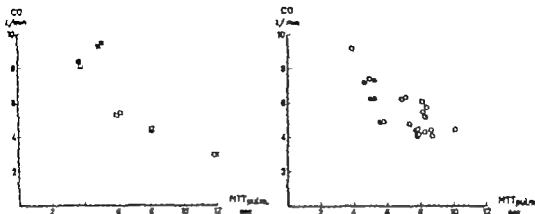
In Group B CO tended to be lower and  $MTT_{pulm}$  longer than in Group A though this rule was not without exceptions.

Comment: The widely used cardiac index requires (i) that CO must be positively and linearly correlated to BSA and (ii) that the line of regression must pass the

origin. Biological relations between factors both of which change during bodily growth are seldom linear within the total range of the factors but may be linear within parts of the region of regression, as ex-



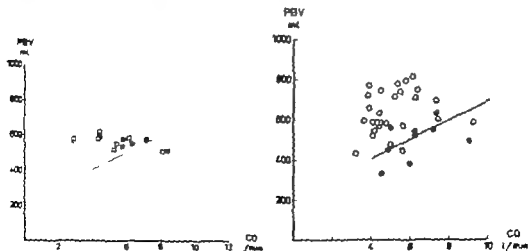
19 Mean pulmonary transit time plotted against body surface area in Group A. The correlation coefficient ( $r = 0.1$ ) is not significant;  $MTT_{pulm}$  averages 4.83 seconds and the standard deviation is 18 per cent thereof.



20 Cardiac output plotted against  $MTT_{pulm}$  in the old (left diagram) and the new (right diagram) series. Filled symbols represent Group A and open symbols Group B.

emplified by CASSEL & MORSKIS (16) analysis of the association between  $TBI$  and  $BSA$ . Hence it should be borne in mind that regression lines for adults and children may not be alike. TAXER (130) theoretically evaluated those errors resulting when the last of these requirements is not satisfied.

JENNIE *et al* (70) studying the association between  $CO$  and  $BSA$  in normal children and adults, assumed the regression would be linear throughout the series as a whole the result being a regression line passing close to the origin. However their diagram shows that the regression hardly could have been linear throughout



21  $PBV$  plotted against  $CO$  in the old (left diagram) and the new (right diagram) series. Filled symbols represent Group A and open symbols Group B. The regression line for Group A ( $PBV = 48CO - 217$ ) is shown in both diagrams.

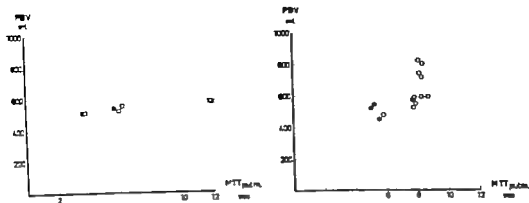


Fig. 2.  $PBF$  plotted against  $MTT_{pulm}$  in the old (left diagram) and the new (right diagram) series. Filled symbols represent Group A and open symbols Group B.

Apparently a regression line for adults would be approximately linear and intersect the abscissa ( $BSA$ ) far from the origin somewhere between  $+1$  and  $+1.5$   $m^2$  while a regression line for children only would have a deviating course. REEVES *et al* (11\*) using Fick's method, presented similar results in the form of a diagram which seems to justify a corresponding reinterpretation. Thus a regression line for adults — subjects with  $BSA$  greater than about  $1.4$   $m^2$  — would seem to meet the abscissa ( $BSA$ ) somewhere between  $+1$  and  $+1.5$   $m$  but the children caused the line to bend towards the origin. These reinterpretations are in good agreement with the findings in Group A, whose regression line intersects the abscissa to the right of the origin at  $BSA$   $0.8$   $m^2$ . While the definitive answer to the question of how  $CO$  normally is associated with  $BSA$  or indeed body size must await future studies, there is some reason to deprecate the uncritical use of the cardiac index in adults.

The fact that the measured  $MTT_{pulm}$  in Group A was independent of  $BSA$  sug-

gests that those factors which control  $MTT_{pulm}$ ,  $PBF$  and  $CO$  have proportionately similar associations with  $BSA$  causing  $BSA$  to cancel out and leaving  $PBF/CO$  independent thereof. Thus when the regressive expressions for  $PBF$  ( $687$   $BSA - 683$ ) and  $CO$  ( $6.98$   $BSA - 5.61$ ) are inserted in the formula  $MTT_{pulm} = PBF/CO$  and various  $BSA$  values are tested, it is found that as  $BSA$  varies between the extremes of  $1.43$  and  $2.07$   $m^2$  in Group A  $MTT_{pulm}$  changes only  $0.9$  seconds.

One would expect  $MTT_{pulm}$  for normal subjects to be closely similar to  $MTT_{pulm}$  for Group A, that is  $4.88 \pm 0.86$  seconds. This agrees with the results reported by GIBBY *et al* (51) who found that 17 patients without cardiovascular disease and with  $BSA$  from  $1.83$  to  $1.98$   $m^2$  had a mean  $MTT_{pulm}$  of  $5.0$  heart cycles with a variation coefficient of 1 per cent corresponding to  $4.6 \pm 0.53$  seconds. They also found a positive correlation ( $p < 0.001$ ) between  $PBF$  and cardiac output, the regression equation ( $PBF = 53$   $CO + 123$ ) being similar to that in Group A.

Among the patients in Group B five from the old series deviated from the others (Figs 20 and 21) and were characterized by short  $MTT_{pulm}$ , low  $CO$  and consequently low  $PBI$ . Four of these patients either had obstructive lung disease and mitral stenosis (Nos. 23 and 31) or were in functional group IV (Nos. 10 and 25) after progressive exacerbation over a period of many years. In such cases one may surmise that  $PBV$  reducing factors are prominent.

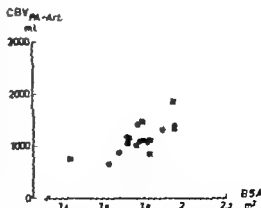
From the formula  $MTT_{pulm} = PBI/CO$  it is obvious that if  $PBI$  rises while  $CO$  remains unchanged or falls — as probably is the case in the early stages of pulmonary venous hypertension —  $MTT_{pulm}$  will become longer than normal. If the disease has progressed to the point where obliterative vascular lesions have reduced sharply the  $PBI$  then the cardiac output will probably be subnormal too. And if now both  $PBI$  and  $CO$  deviate proportionately as much from normal,  $MTT_{pulm}$  could theoretically remain normal.

It may be inferred from what has been said above that no predictions are possible with regard to the nature of the association to be expected between the factors  $PBI$ ,  $MTT_{pulm}$  and  $CO$  in series of very heterogeneous patients with left heart disease. The relations may be expected to vary wholly in accordance with the distribution of patients with diseases of different degrees and durations. For example judging by Fig. 21 in the old series there is a positive correlation between  $PBI$  and  $CO$  while apparently there is no corresponding relation in the new series. Furthermore Dock *et al* (23) found no correlation between  $PBI$  and  $CO$  in their series as a whole whereas

a positive correlation did exist between these factors in the series of patients described by McGarry *et al* (80).

## PULMONARY BLOOD VOLUME AND CENTRAL BLOOD VOLUME

The central blood volume ( $CBV$ ) from the pulmonary artery to a systemic artery ( $CBV_{PA-A}$ ) was calculated for the patients in Group A and corrected for the mean transit time through the collecting catheter. Only the first of duplicate determinations was taken into account. The results have been plotted in Fig. 22 showing that  $CBV$  was positively correlated to  $BSA$  ( $r = 0.79$ ;  $p < 0.03$ ).  $CBV$  was also positively correlated to  $CO$  ( $r = 0.48$ ;  $p < 0.03$ ) and to  $SI$  ( $r = 0.01$ ;  $p < 0.03$ ). The mean  $CBV$  was 1.31 litres with a standard deviation of 0.3 litres, the mean  $CBV$  per square metre  $BSA$  was  $0.67 \text{ l/m}^2$  and the range 0.40 to  $1.09 \text{ l/m}^2$ .



22. Central blood volume ( $CBV_{PA-Art}$ ) plotted against body surface area ( $BSA$ ) in Group A. The coefficient of correlation ( $r = 0.79$ ) is significant.

*Comment* The magnitude of  $CBV$  in Group A is in excellent agreement with other investigations where  $OBI_{PA}$  in cardiovascularly normal subjects has been calculated (20 74 76 82). Under normal conditions the average central blood volume as estimated by injection of an indicator into a peripheral vein and blood collection from a peripheral artery varies in different publications between 1.8 and 2.8 litres (5 44 74 8 96) corresponding approximately to 33 to 55 per cent of the total blood volume. Indicator injection in the pulmonary artery yields smaller  $CBI$  corresponding to about 25 per cent of  $TBI$ . Pulmonary blood volume constitutes some 10 per cent of the total blood volume and up to barely half the central blood volume depending on where the indicator is injected.

Under normal conditions at rest it has been shown that  $CBI$  is positively correlated to  $CO$  and to  $SV$  (45 49 64 71 96 141) as was the case in Group A. Although the demarcations of the central blood volume admittedly are impossible to define in anatomical terms (83 146) they presumably vary little among normals examined by the same standardized technique. Most likely therefore central blood volume is positively correlated to

body size and the use of the central blood volume index ( $CBV/m^2$ ) presupposes this. The strong and significant correlation between  $CBV$  and  $BSA$  in Group A can be assumed to portray conditions in normal subjects. With respect to  $PBV$  as well as to  $CBI$  this writer is of the opinion that the positive correlations to  $CO$  and to  $SV$  merely signify that each of these four factors ( $PBI$   $CBI$   $CO$   $SV$ ) is positively correlated to body size. The problem whether these haemodynamic factors interact in any way cannot be solved by analyses of the type used in the present study but requires investigations in which these factors are caused to change in order to ascertain whether changes in any one are correlated to changes in one or more of the others.

Considering that pulmonary blood volume constitutes merely a small fraction of the central blood volume no deductions about the former can be drawn from estimations of the latter. The physiological background of observed changes in central blood volume cannot be defined since they may represent either real changes in capacity whose location cannot be established, or merely a redistribution of flow in the peripheral arteries (83 88).

## SUMMARY

The aims of the investigation were to examine the experimental premises for pulmonary blood volume (PBV) estimation with the aid of the double indicator technique to assess the reproducibility of this technique, and to analyse the magnitude of pulmonary blood volume and its associations with various clinical and physiological factors at rest.

### Methods

Two dye indicators, bromsulphalein (BSP) and cardiogreen (CG) were injected simultaneously either of them into the pulmonary artery and the other into the left atrium. Blood was collected from a systemic artery by fractionated sampling. Pulmonary blood volume was estimated as the product of cardiac output and pulmonary mean transit time factors calculated from the indicator dilution curves according to Hamilton's principles. Often cardiac output was measured by Fick's method too. Pressures were recorded in the pulmonary artery, left atrium and a femoral artery.

### Clinical Material

Pulmonary blood volume was measured in two groups of patients of both sexes: the old series with 34 patients and the new series with 38 patients. Most of the patients had cardiovascular diseases involving the left side of the heart. Different degrees of disease were represented.

### Evaluation of Method

The dye procedure was attended by immediate minute decreases in mean pulmonary arterial pressure and mean left atrial pressure. Conceivably caused by the indicator injections and/or blood loss the haemodynamic alterations probably were too small to invalidate the pulmonary blood volume determination.

Cardiac output was determined in a separate group of patients by injection into the same catheter of both bromsulphalein and cardiogreen. The results agreed closely and revealed no systematic differences between the two methods. Analysis of the pulmonary blood volume measurements disclosed no systematic differences between the simultaneous cardiac output determinations by indicator injection in the pulmonary artery and the left atrium or between the average of these two determinations and concomitant estimations by Fick's method. Nor did duplicate cardiac output estimation by injection of either of the two indicators into the pulmonary artery differ significantly from simultaneous duplicate estimations by injection of the other indicator into the left atrium.

The results of the cardiac output determinations are discussed and it may be inferred that bromsulphalein and cardiogreen are equivalent indicators that neither bromsulphalein nor cardiogreen vanishes from the blood stream during its passage through the lungs that bron-

chopulmonary shunts were unlikely to be of quantitative importance in the present study that indicator injection into the left atrium yields correct cardiac output estimations, and that the mean of the two flow determinations associated with pulmonary blood volume measurement does not on an average deviate from the actual flow

Duplicate pulmonary blood volume estimations in 17 patients revealed the mean ratio of the first to the second estimation to be 1.02 and the standard deviation 0.10. The mean ratio of the first to the second estimation of pulmonary mean transit time was 1.00 and the standard deviation 0.11. The mean difference between the first and second cardiac output determinations was not significant and the standard deviation was 0.47 l/min (8.3% of the mean).

Potential sources of error in the double indicator method are discussed, and evidence is presented suggesting that the arterial collecting catheter introduced no error in the estimation of cardiac output, pulmonary mean transit time and pulmonary blood volume.

#### *Pulmonary Blood Volume and Its Relations to Other Factors at Rest*

The analyses comprised 33 patients from the old series and 36 from the new. 3 patients having been eliminated for procedural reasons. Pulmonary blood volume varied between 187 and 822 ml, the mean being 577 ml. The patients were divided into two groups depending on whether or not they satisfied four criteria: (i) functional group I or II; (ii) sinus rhythm; (iii) systolic pulmonary arterial

pressure at most 30 mm Hg and mean left atrial pressure at most 13 mm Hg at rest; and (iv) roentgenologically normal appearance of the pulmonary vessels. Patients satisfying these criteria constituted Group A ( $n = 20$ ) and the remainder Group B ( $n = 19$ ). In the light of the stipulated criteria and pressure and flow data, the pulmonary haemodynamics, including pulmonary blood volume in Group A were presumed to be closely similar to normal conditions at rest. The patients in Group B were on the whole in more advanced stages of disease.

*Findings in Group A.* Pulmonary blood volume was positively correlated to body size. The correlation to stature ( $r = 0.81$ ) was of the same order as that to body surface area ( $r = 0.84$ ) but weight was a poorer predictor of pulmonary blood volume ( $r = 0.66$ ). Body surface area was chosen as the body size parameter to be used in subsequent analyses. The regression of pulmonary blood volume (PBF) on body surface area (BSA) fits the equation  $PBF = 687BSA - 683$ . Pulmonary blood volume varied from 333 ml to 95 ml, and body surface area from 1.42 to  $2.0 \text{ m}^2$ , the expected mean pulmonary blood volume corresponding to 1.73  $\text{m}^2$  BSA being 506 ml.

Pulmonary blood volume was positively correlated to stroke volume ( $r = 0.32$ ) and to cardiac output ( $r = 0.43$ ). Both stroke volume and cardiac output were also positively correlated to body surface area (stroke volume  $r = 0.78$ , cardiac output  $r = 0.62$ ) unlike pulmonary mean transit time which was independent of body surface area ( $r = 0.15$ ) and averaged 4.83 seconds with a standard deviation



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## APPENDIX

Clinical and laboratory data for patients in the old series (Table 10) the new series (Table 11) and the group where both indicators were injected into the same catheter (Table 12)

### KEY TO ABBREVIATIONS

*Diagnoses* MIS = mitral stenosis, MII = mitral insufficiency AoS = aortic stenosis, AoI = aortic insufficiency SubAoS = subaortic stenosis, Ao.coart. = aortic coarctation, TI = tricuspid insufficiency Constr.peric = constrictive pericarditis Cardioscl. = cardiosclerosis (ischaemic heart disease) Hpt = systemic hypertension OLD = obstructive lung disease, Cardiomyop. = cardiomyopathy Norm. haemodyn. = normal haemodynamics without signs of cardiovascular disease.

*Heart Rhythms* S.R. = sinus rhythm, A.F. = auricular fibrillation A. V bl. = total atrioventricular block, V.E.S. = ventricular extrasystoles, A.Flut. = atrial flutter

*Indicator Injection Sites* PA = pulmonary artery LA = left atrium RA = right atrium VCI = inferior caval vein.

*Indicators* BSP = bromsulphalein, CG = cardiogreen.

*Pulmonary Blood Volume Estimation* MTT <sub>pulm</sub> = mean transit time through the lungs, PBV = pulmonary blood volume.









